The association between phthalate exposure and asthma

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Abstract  Asthma is a chronic inflammatory disorder of the airway, characterized by airway hyperresponsiveness. It is a disabling disease with an increasing prevalence, resulting in heavy social and economic burdens worldwide. Humans are extensively exposed to phthalates, and many epidemiological studies have shown a relationship between phthalate exposure and asthma in recent decades. Earlier experimental studies focused on inflammatory cells, demonstrating the adjuvant effects, immunomodulatory effects, or immunosuppressive effects related to phthalate exposure. Recent studies have shown that phthalates may have a direct effect on airway epithelial cells and contribute to airway remodeling, which is the cardinal pathologic characteristic of chronic asthma, with a high correlation with disease severity. Through these efforts, phthalates have been recognized as important environmental factors in the pathogenesis of asthma, but further studies are still required to elucidate the detailed mechanism. This review discusses the current status of human exposure to phthalates in Taiwan and summarizes the epidemiological and experimental evidence related to the roles of phthalate exposure in the development of asthma and associated diseases.

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Introduction

Asthma is a chronic inflammatory disorder of the airway with an increasing prevalence worldwide over the past few decades. It is also an expensive disease, and has aroused significant public health concern. Airway remodeling is the cardinal pathological characteristic of chronic asthma, and the degree of airway remodeling correlates well with disease severity. In recent years, plasticizers, especially...
Phthalates, have been recognized as important environmental factors in the pathogenesis of asthma. Besides many epidemiological studies showing a relationship between phthalate exposure and asthma in recent decades, many experimental studies have demonstrated various adjuvant or inflammatory responses of inflammatory cells related to phthalate exposure. Recent studies have shown that phthalates may also contribute to airway remodeling. The Taiwan plasticizer scandal in 2011 re-aroused concern regarding the health effects of phthalates worldwide, and it is therefore time to re-examine the evidence concerning the health effects of exposure to phthalates. This review focuses on the roles of phthalate exposure in the development of asthma and associated diseases.

Phthalates

Phthalates, or phthalate esters, are esters of phthalic acid (Fig. 1). Since the introduction of phthalates as plasticizers in early 20th century, these industrial chemicals have become the most widely used plasticizers, which are added to plastics to increase their flexibility, transparency, durability, and longevity. The most commonly used phthalates are di-(2-ethylhexyl) phthalate (DEHP), di-isononyl phthalate (DiNP), and di-isodecyl phthalate (DiDP) [1,2].

Human exposure to phthalates

Humans have extensive exposure to phthalates nowadays, as these chemicals are the main plasticizers for polyvinyl chloride (PVC), one of the most important plastic materials [3–5]. Phthalates are ubiquitously present in our daily life, being present in flexible plastics, toys, food packages, pharmaceutical pills, paints, personal care products, cosmetics, PVC flooring, and so on [6]. Because phthalates are not chemically bound to the PVC molecules in plastics, they can easily leach out and evaporate into food or the environment [7]. Ingestion is traditionally believed to be the major route of exposure, although other routes, including inhalation, dermal, and parenteral routes, have also been recognized [1].

As DEHP is the phthalate plasticizer used in almost all PVC medical devices, leaching of DEHP from PVC medical devices and ultimate tissue deposition have been documented since the late 1960s [6,8,9]. For example, DEHP has been detected in the air delivered by PVC tubing used in respiratory therapy [10]. It has also been reported that the quantity of DEHP delivered to the patient from physiologic saline solution contained in a plastic PVC bag was 0.126 mg/L, increasing to 0.588 mg/L after shaking [11]. Other medical devices that may contain DEHP include intravenous bags and tubing, catheters, blood bags and infusion tubing, enteral nutrition feeding bags, nasogastric tubes, peritoneal dialysis bags, and tubing used in cardiopulmonary bypass procedures, extracorporeal membrane oxygenation, and during hemodialysis [9].

Current human exposure to phthalates in Taiwan

Exposure to phthalates is usually quantified by detecting urinary phthalate metabolites. A Taiwanese study revealed that more than 90% of samples from 60 subjects contained detectable monomethyl phthalate, mono-n-butyl phthalate (MnBP), and mono-(2-ethylhexyl) phthalate (MEHP) [12]. Estimated from the quantities of urine metabolites, the medium daily intake of DEHP in the Taiwanese subjects was 0.0339 mg/kg/day, which is about three times that reported in a German study [12–14]. Based on these data, 85% of the subjects had an estimated daily intake of DEHP over the reference dose of the United States Environmental Protection Agency (0.02 mg/kg/day), and 37% of subjects

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**Figure 1.** Common phthalates. Abbreviations: BBzP, butyl-benzyl phthalate; DEHP, di-(2-ethylhexyl) phthalate [also known as bis(2-ethylhexyl) phthalate (BEHP) or di-octyl phthalate (DOP)]; DEP, di-ethyl phthalate; DiBP, di-iso-butyl phthalate; DiDP, di-isodecyl phthalate; DiHP, di-iso-hexyl phthalate; DiNP, di-iso-nonyl phthalate; DnBP, di-n-butyl phthalate; DnOP, di-n-octyl phthalate.
had a daily intake of DEHP over the tolerable daily intake defined by the European Union Scientific Committee for Toxicity, Ecotoxicity and the Environment in 1998 (0.037 mg/kg/day) [12]. In another study, a high content of phthalate metabolites was detected in urine samples collected from pregnant Taiwanese women, and the median levels of MnBP, monoethyl phthalate, and MEHP were 81.8 ng/ml, 27.7 ng/ml, and 20.6 ng/ml, respectively [15].

Taiwan plasticizer scandal in 2011

In May 2011 the largest food scandal in Taiwan was reported. Initially, a quality inspector discovered that the density of plasticizer in some raw materials of probiotics far surpassed the standard in a routine check [16]. Further investigation revealed that DEHP and DiNP were inappropriately used as cloudy agents instead of palm oil by some food manufacturers to lower costs and prolong preservation time [17–20]. This news generated worldwide attention, and the Taiwanese government soon initiated seizures of contaminated foods, including beverages, breads, and jams, and announced a ban from exporting [19–23]. The products were all recalled, examined, and immediately destroyed [16,19,20,24]. This scandal highlighted the issue of food safety and aroused the public’s attention with regards to the health effects of phthalates.

Phthalates association with asthma

Asthma is a chronic inflammatory disorder of the airways. Epidemiologic studies usually rely on questionnaire assessments of symptoms, clinical diagnosis by physicians, and the use of related medications. Although highly sensitive and specific diagnostic tests are currently unavailable, there is no doubt that asthma is a serious public health problem worldwide, with an estimated 300 million affected individuals, including people in all age groups [25]. The prevalence varies widely between countries, ranging from 1% to 18% of the population, which may be partially attributed to the lack of a precise and universally accepted definition [25–29]. Nonetheless, the prevalence has been rising in most parts of the world over the past few decades [25–27,29].

Asthma is a costly illness. A national survey in the United States for the years 2002–2007 showed that the estimated total cost (in 2009 US dollars) of asthma to society, including medical expenses ($50.13 billion per year in 2007), loss of productivity resulting from missed school or work days ($3.76 billion per year in 2007), and productivity loss due to death ($2.15 billion per year in 2007), was $56 billion in 2007, a $3 billion (5.7%) increase from 2002, and the estimated medical expenses associated with asthma were $3,259 per person per year (in 2009 US dollars) [26,30]. Another study showed that adults with asthma experienced higher healthcare use and comorbidity and incurred an additional cost of $1,907 (in 2008 US dollars) annually [31,32]. Although most patients with asthma can be asymptomatic under appropriate medical control, some patients have poorly-controlled asthma, which may result in increased emergency department visits, hospitalizations, and medical costs [26,30]. In addition, about 4000 deaths per year in the United States are attributed to asthma [30]. Therefore, the costs of asthma are substantial, necessitating further research in this field.

Asthma is a complex disease resulting from interaction between host factors and environmental factors. A variety of risk factors have been identified, including genetic susceptibility, obesity, gender, infections, atopy, tobacco smoke, occupational sensitizers, air pollution, and other environmental exposure [25].

The major clinical features of asthma include airway inflammation, airway hyper-responsiveness, mucus hypersecretion, and intermittent reversible airway obstruction [33,34]. Patients with asthma usually present with repeated, variable, intermittent attacks of breathlessness, cough, wheezing, or chest tightness as a result of intermittent bronchoconstriction in the setting of airway hyper-responsiveness and mucous hypersecretion [33].

Airway remodeling is the cardinal pathological characteristic of chronic asthma, and the degree of airway remodeling correlates well with disease severity [35–38]. Many cells and cellular elements play a role. The structural changes in airway remodeling include loss of epithelial integrity (epithelial cell erosion), subepithelial fibrosis, goblet cell hyperplasia/metaplasia, submucosal gland enlargement, airway smooth muscle hyperplasia and hypertrophy, and microvascular changes (increased angiogenesis mostly) [39–42]. These changes may result from repeated or continuous airway inflammation induced by repeated exposure to the allergen [34,43].

The role of phthalate exposure in the development of asthma

Although phthalate exposure has been traditionally thought to occur mostly through ingestion, other routes, including dermal, parenteral, and particularly inhalation, may also play important roles [1,44,45]. Much evidence, including case reports, case series, epidemiologic studies, and mechanistic toxicology studies, has demonstrated that phthalate emissions from PVC materials may increase the risk of asthma and allergies [1,44,45].

Epidemiologic evidence

In the 1970s, cases of asthma with possible relationships with fumes from hot-wire cutting of PVC film or from thermo-activated price labels were reported as “meatwrapper’s asthma” [46–49]. This led to several epidemiologic studies, which found that exposure may be associated with a higher prevalence of asthma, allergy, or related respiratory symptoms [50–54]. Some studies even found that exposure was associated with decline in lung function [50,52], while others showed no significant change [53,54]. Later, cases of asthma with a possible relationship with occupational exposure to di-n-octyl phthalate (DnOP), smoke inhalation from a residential fire, or exposure to unleaded PVC resin dust were also reported [55–57]. A cohort study showed that firefighters exposed to burning PVC had more frequent and severe respiratory symptoms [58]. An observational study in a PVC processing plant found
that workers exposed to PVC thermal degradation products and phthalic acid esters had more upper airway symptoms than unexposed workers, while no significant differences in lung function were noted [59]. A study involving four Swedish geriatric hospitals showed that asthma symptoms may be associated with increased humidity in concrete floor constructions and emission of 2-ethyl-1-hexanol (2-EH), an indicator of dampness-related degradation of DEHP [60]. A later study in an office building with severe dampness and 2-EH in indoor air found that the workers’ respiratory symptoms and need for medications decreased after interventions, including careful removal of the plastic floor covering [61]. In a population-based incident case–control study systematically recruiting all new cases of asthma during a 2.5-year-study period and randomly selected controls in Finland, the risk of asthma was found to be related to the presence of plastic wall materials and wall-to-wall carpets at work [62].

There have also been many epidemiological studies in children. Since the late 1990s, epidemiological studies regarding the possible relationship between phthalates and airway diseases in children have been conducted, mostly in northern Europe. The presence of PVC materials, especially PVC flooring, has been associated with bronchial obstruction in children in case–control studies [63,64]. Subsequent cross-sectional questionnaire investigations also showed significant associations between PVC flooring or plastic wall material and airway symptoms in children [65–67]. Later case–control studies further demonstrated that the concentration of DEHP in indoor dust was significantly associated with case status and asthma [68,69]. Recently, in a large cohort study in Sweden, parental reporting indicated that PVC flooring in the child’s and parents’ bedroom when the child was aged 1 year to 3 years was significantly associated with incidence of asthma 5 years later [70].

These epidemiologic studies provide evidential clues indicating a relationship between phthalate exposure and asthma.

Mechanistic toxicologic evidence — in vivo studies

Studies addressing the putative ability of phthalates to act as adjuvants for immune responses have been investigated almost exclusively in murine models, especially BALB/c mice (mouse strain most susceptible to the development of IgE-mediated reactions) [1,2,44]. Immune responses underlying the development of allergic sensitization involving antigen-presenting dendritic cells, Th2 cells, mast cells, and eosinophils, and the production of specific IgE, are hallmarks of allergic asthma [1,2,44]. In mice, Th2 cells promote IgG1 and IgE, and Th1 cells promote IgG2a [44]. Because specific IgE is difficult to measure accurately due to its presence in small amounts, the total plasma level of IgE or IgG1 is commonly used as a surrogate marker [2,44]. However, although IgG1 is produced through similar mechanisms, the IgG1 level does not always exactly mirror the IgE responses, so careful interpretation of the data is required [2].

The adjuvant properties of phthalates appear to be influenced markedly by the administration route and the type and dose of the tested compound [1,2,44]. In initial studies, phthalates were administered by subcutaneous injection [71–74]. Subcutaneous exposure to DEHP effectively augmented the antibody response of IgG1, but not IgE, to ovalbumin [71]. When various monoesters (the primary hydrolytic metabolites of phthalate diesters), including MEHP, mono-n-octyl phthalate (MnOP), mono-isononyl phthalate (MiNP), mono-iso-decyl phthalate (MiDP), mono-benzyl phthalate (MBnP), and MnBP, were tested, various effects were observed: an immuno-suppressive effect was observed with MEHP (1000 µg/ml, IgE and IgG1), MnOP (1000 µg/ml, IgE and IgG1), MiNP (1000 µg/ml, IgE and IgG1) and MiDP (100 µg/ml, IgE and IgG1); an adjuvant effect was observed with MEHP (10 µg/ml, IgE), MnOP (100 µg/ml, IgE and 10 µg/ml, IgG1) and MiNP (100 µg/ml, IgE); and no statistically significant immune modulating effect was seen with MBnP and MnBP [72]. Similar variations were also observed in studies of di-n-butyl phthalate (DbnP), DnOP, DnIP and DiDP [73], while benzylbutylphthalate (BBzP) produced no adjuvant effect [74]. The authors postulated that the lengths of the carbon side chains are important in terms of the biological activities in this respect [73]. Subsequent studies using the intraperitoneal route for administration of DEHP and DiNP also showed adjuvant effects [75,76]. These experiments, however, do not reflect the actual conditions of human contact (mainly oral ingestion, inhalation, or topical contact).

To mimic the actual routes of human contact, animal models of phthalate exposure via oral, inhalation, or topical routes were developed. The few reports of oral exposure to DEHP showed conflicting results, and further studies were undertaken [2,44]. Topical exposure to high doses of DEHP, DiNP, di-isohexyl phthalate (DIHP), or BBzP also failed to alter the serum concentration of IgE, despite sufficient percutaneous absorption being confirmed with significantly elevated liver weights [77]. Similar experiments with DEHP showed consistent results [78], while experiments using high topical doses of BBzP (100 mg) resulted in a modest elevation in IgG1, but not IgE [79]. Some studies have used inhalation of aerosols. Repeated exposure to airborne DEHP has been shown to increase the serum IgG1 level (but not IgE level) and the levels of inflammatory cells, including eosinophils, lymphocytes, and neutrophils, in the lung and bronchoalveolar lavage fluid, but the effect is observed only at very high concentrations of DEHP [80]. Repeated exposure to airborne MEHP (a major metabolite of DEHP) has nearly identical adjuvant effects, but at lower doses than those required for DEHP [81]. Another study showed that one-time, 60-minute, exposure to airborne MEHP resulted in acute airway irritation and an increased number of macrophages in the bronchoalveolar lavage fluid, only at high levels of exposure [82].

A human study analyzing the response of subjects allergic to house dust mites challenged with house dust containing either low or high levels of DEHP was also performed [83]. Although no effect on symptom scores was noted, challenges with house dust containing low levels of DEHP increased eosinophil cationic protein, granulocyte-colony-stimulating factor (G-CSF), interleukin (IL)-5, and IL-6, whereas challenges with house dust containing high
levels of DEHP decreased G-CSF and IL-6 [83]. These observations were interesting, but as the authors acknowledged, the study design used a short-term exposure protocol that made it difficult to extrapolate to the pattern of actual environmental exposure [2].

Although the heterogeneity in the study designs, including routes of administration, exposure times, and sensitization protocols, makes it difficult to make direct comparisons, the overall picture of these experimental studies suggests that several phthalates may have adjuvant effects on Th2 responses, immunomodulatory effects, or immunosuppressive effects under different conditions [1,2,44].

The route and the dose matter. Significant responses are obtained from subcutaneous or intraperitoneal administration, which do not reflect the actual route of human exposure to phthalates [2]. The results from animal studies suggest that the levels of phthalates encountered in the realistic environment do not have an adjuvant effect or induce allergic lung inflammation, and are therefore unlikely to be a major factor contributing to the increased incidence of asthma and allergy in the developed world [79,80]. Furthermore, most experiments showed only IgG1 responses, with the absence of an IgE response [2,44]. As allergic diseases in humans are mainly mediated via IgE, the results from these animal studies are far from clinically applicable.

Mechanistic toxicologic evidence — in vitro studies

Attempts have also been made to address the in vitro effects of various phthalates on a variety of cells, focusing on immunologic cells [1,2,44]. It has been demonstrated that DEHP may enhance differentiation of bone marrow-derived dendritic cells (BMDC) with an increased antigen-presenting activity and an increased T-cell proportion in splenocytes with increased IL-4 production, whereas it may activate differentiated BMDC at low doses and suppress differentiated BMDC at high doses, with no significant changes in antigen-presenting activity [84]. In primary murine lymph node cells, DEHP and DiNP may enhance IL-4 production [75,85]. Further experiments using a murine thymoma cell line (EL4) suggested that both DEHP and DiNP enhanced IL-4 production via stimulation of the binding activity of the transcription factor NF-AT to the IL-4 gene promoter [75]. It has also been found that a glycoprotein isolated from Cudrania tricuspidata Bureau (CTB glycoprotein) has a strong inhibitory ability towards DEHP-induced IL-4 production in primary-cultured murine T lymphocytes [85]. Some studies have also demonstrated the effects of MEHP on inducing growth arrest and apoptosis of bone marrow B cells [86–88].

Studies discussing the effects of phthalates on monocytes and macrophages have revealed complex results. Although a study with primary alveolar macrophages from rabbits showed that DEHP may potentiate phagocytosis and the release of lysosomal enzymes [89], another study demonstrated limited potentiation of phagocytosis and a potent inhibitory effect of bacteriocidal capacity [90]. A study using primary human monocytes and neutrophils from healthy volunteers demonstrated that metabolites of DEHP (MEHP, 2-EH, and phthalic acid) may suppress oxidative respiratory metabolism and superoxide generation at a low pH level, whereas these effects were very weak at a physiological pH level [91]. Using a rather different approach, monophthalates showed no effect on the expression of cytokines from monocytic cell line THP-1 and peripheral blood mononuclear cells (PBMCs), except for increased IL-4 expression in PBMCs from allergic subjects treated with MnBP [92]. In an ex vivo study, potentiation of lipopolysaccharide (LPS)-induced TNF-α production was noted in primary peritoneal macrophages from mice treated with subcutaneous BBzP in advance, whereas an in vitro study demonstrated that BBzP may inhibit LPS-induced TNF-α production in the murine macrophage cell line RAW264 [93]. Consistent with the potentially immunosuppressive effects of innate immunity, another study also demonstrated that some phthalates may inhibit LPS-induced activation of the IFN-β promoter [94].

Besides affecting gene expression of the immune cells, phthalates may modulate the inflammatory response rapidly via a nongenomic cellular mechanism [44]. DEHP may increase the expression of CD11b, an integrin important for adhesion and migration of inflammatory cells from vessels to the inflammatory site, in primary cultured blood from both humans and rats within a few minutes [95]. Studies using the RBL-2H3 mast cell line revealed that DnBP, DiBP, and DEHP potentiated antigen-induced degranulation through increased mobilization of intracellular calcium ions [96]. Short-term exposure to DEHP and MEHP was shown to potentiate IgE-mediated histamine release from primary human basophils cultured from non-atopic subjects, suggesting a possible adjuvant effect on the elicitation of allergic responses via nongenomic mechanisms [97]. Interestingly, although the role of eosinophils in the pathophysiology of asthma and allergic disease has been well documented, and increased eosinophils in the lung and bronchoalveolar lavage fluid have been demonstrated in an animal model of exposure to aerosol DEHP, no in vitro data regarding the direct effects of phthalates on eosinophils are available to date [44].

There are also few reports addressing the direct effect of phthalates on airway epithelial cells and their active involvement in the pathogenesis of asthma. In a concentration range of around 10 to 100 mg/L, some mono-phthalates (MnBP, MnBP, MnOP, MEHP, MnBP, and MnDP) may promote production of proinflammatory cytokines IL-6 and IL-8 from a human airway epithelial cell line (A549), whereas suppressive effects were noted at higher concentrations [98]. A recent study further demonstrated a complex mechanism of phthalate-associated asthma, focusing on the role of airway epithelial cells and their interaction with airway smooth muscle cells in airway remodeling (Fig. 2) [3]. In this study, human bronchial epithelial cell lines were treated with BBzP, DEHP, DNBP, and DEP, and the conditioned media were harvested. Treatment with various conditioned media increased the proliferation and migration of bronchial smooth muscle cells, which were major features in the airway remodeling, and also increased the expression of many inflammatory and chemotactic factors, including IL-8, CXCL5, CXCL2, CXCL3, IL-6, intercellular adhesion molecule 1 (ICAM-1), and IL-1β, in the bronchial smooth muscle cells. Further
investigation confirmed that phthalate exposure enhanced the airway epithelial cell production of inflammatory cytokines IL-8 and RANTES, which subsequently induced the proliferation and migration of bronchial smooth muscle cells. Moreover, (6)-shogaol, (6)-gingerol, (8)-gingerol, and (10)-gingerol, which are major bioactive compounds present in Zingiber officinale, suppressed the phthalate-induced effects of airway remodeling. This study was quite unique, not only in demonstrating that inflammatory cytokines produced by bronchial epithelial cells after exposure to phthalates contributed to airway remodeling by increasing the migration and proliferation of human bronchial smooth muscle cells and promoting the secretion of various inflammatory and chemiotaxic cytokines from human bronchial smooth muscle cells, but also in revealing that ginger may reverse phthalate-induced airway remodeling [3]. The detailed mechanisms, however, require further investigation [3].

Other health effects of phthalates

In addition to asthma and allergic diseases, phthalates have been associated with many health problems. As a kind of endocrine disrupter chemical, also known as environmental hormones, this group of xenobiotic substances is able to interfere with normal homeostasis and metabolism [45,99]. Great concerns have been raised regarding their anti-androgenic activity, causing testicular dysgenesis, decreased sperm concentration and worsened semen quality, infertility, and decreased testosterone levels [7,45,100]. Prenatal exposure to phthalates may also result in preterm delivery, congenital anomaly, decreased anogenital distance, hypospadias, and decreased masculine play behaviors among male infants [4,5,7,45,101,102]. In females, phthalate exposure is associated with early puberty, especially thelarche, endometriosis, adenomyosis, leiomyoma, and even breast cancer [45,103–105]. Although early studies focused on the estrogenic activity of phthalates in the pathogenesis of breast cancer, a novel estrogen-independent oncogenic mechanism of phthalates in breast cancer, involving the AhR/HDAC6/c-Myc signaling pathway, has been recognized recently [105]. In addition, significant mild negative correlations were found between the levels of serum thyroid hormones (both free T4 and total T4) and the level of urinary phthalate metabolites in the urine of pregnant women [15]. Furthermore, recent studies have also recognized possible associations between phthalate exposure in children and the development of autism spectrum disorders, although further extensive confirmation is warranted [106].

Using the Comparative Toxicogenomics Database, a toxicogenomic study analyzing the curated interactions between 16 phthalates and a variety of genes/proteins found that the top three phthalate toxicity categories were cardiotoxicity, hepatotoxicity, and nephrotoxicity, and the top 20 diseases included cardiovascular, liver, urologic, endocrine, and genital diseases [6]. The authors concluded that further studies were needed to confirm the significance of the associations, especially the newly-discovered cardiotoxicity and nephrotoxicity [6].

Conclusion

As phthalates are used extensively in our daily life, the effect of phthalate exposure on health has become an extremely important issue. In addition to their notorious endocrine-disrupting activities, their contribution to the pathogenesis of asthma and allergic diseases has been gradually recognized in recent years. As mentioned above, much epidemiologic evidence addresses the relationship between phthalate exposure and asthma and allergic diseases. Although conflicting results exist, most experimental studies address the adjuvant effects of phthalates in immune responses. A recent study directly investigated the effects of phthalates in airway epithelial cells and the ensuing cell—cell interaction with bronchial smooth muscle cells, simulating the pathophysiology of airway remodeling in asthma and inflammatory airway diseases. These data may assist in elucidating how phthalates induce asthma and allergic diseases.

Nonetheless, the whole picture is still far from being totally understood. Most of the studies discussing the health effects of phthalates are epidemiological studies, and few experimental studies have been performed. Furthermore, few studies have addressed the detailed molecular signaling mechanisms underlying the health effects of phthalates. In order to confirm the causative effects of phthalates in various diseases, further investigation, including both in vivo and in vitro studies, is warranted.

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