The Impact of Bisphenol A and Phthalates on Allergy, Asthma, and Immune Function: a Review of Latest Findings

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Abstract In recent years, the impact of environmental exposure to chemicals and their immunological effects, including the development of allergy, has been a topic of great interest. Epidemiologic studies indicate that exposure to endocrine-disrupting chemicals produced in high volumes, including bisphenol A (BPA) and phthalates, is ubiquitous. The links between their exposure and the development of allergy, asthma, and immune dysfunction have been studied in vitro, in vivo, and through human cohort studies. The purpose of this review is to examine the current body of research and to highlight deficits and strengths of current findings. Emerging science indicates that deleterious immunologic changes, including increased propensity to develop wheeze, allergy, and asthma after dietary and inhalation exposure to these chemicals, may be occurring.

Keywords Bisphenol A · Phthalates · Allergy · Asthma · Immunotoxicity · Wheeze

Abbreviation

BBzP	Butyl benzyl phthalate
BPA	Bisphenol A
CCCEH	Columbia Center for Children's Environmental Health
DBP	Dibutyl phthalate
DEHP	Diethyl hexyl phthalate
DEP	Diethyl phthalate
DIDP	Diisodecyl phthalate
DINP	Diisononyl phthalate
DMP	Dimethyl phthalate
DnBP	Di- <i>n</i> -butyl phthalate
DNOP	Di- <i>n</i> -octyl phthalate
EDC	Endocrine-disrupting chemical
FeNO	Fractional exhaled nitric oxide
GALT	Gut-associated lymphoid tissue
iNOS	Inducible nitric oxide synthase
MBzP	Mono benzyl phthalate
NHANES	National Health and Nutrition Examination Survey
OVA	Ovalbumin
PVC	Polyvinyl chloride
ROS	Reactive oxygen species
Th	T helper
TSLP	Thymic stromal lymphopoietin

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Introduction

According to the World Health Organization's report in 2007, at least 20 % of the world's population was estimated to suffer

from an allergic condition (http://www.euro.who.int/__data/assets/pdf_file/0012/96996/3.1.pdf?ua=1). Over recent years, the production and use of plastics and polycarbonates, which frequently contain bisphenol A (BPA) and phthalates, have risen dramatically. In light of these observations, the potential impact of exposure to these chemicals on the rising prevalence of atopy and allergy becomes an intriguing question. In this review, we will examine the recent data on BPA and phthalates as they pertain to the development of allergy and perturbed immunologic health, including the sources of exposure, proposed mechanisms of action, and compelling human cohort studies.

Bisphenol A

BPA is a 4,4-isopropylidenediphenol 2,2-bis(4-hydroxyphenyl)propane. It contains two functional phenol groups that allow the chemical to interact with estrogen and androgen receptors as both an agonist and antagonist [1]. This classifies BPA as a xenoestrogen (environmental estrogen). Its ability to stimulate the estrogen receptor further classifies it as an endocrine-disrupting chemical (EDC) [2, 3]. The estrogenic activity of BPA has been estimated to be 1/1000 to 1/10,000 of that of 17 β -estradiol [4].

BPA is contained in polycarbonate plastics and epoxy resins and is used in the production of polyvinyl chloride [5]. Items containing BPA include children's toys, dental sealants, lining of water pipes, food and beverage containers such as plastic water bottles, food packaging, and the inner coating of cans and bottles [2, 6, 7]. It is estimated that, each year, greater than 15 billions pounds of BPA are produced and over 100 tons are released into the atmosphere [3]. The primary route of exposure of BPA is oral, mainly from eating or drinking from products containing BPA. Other potential exposures include inhalation from dust particles and atmospheric exposure [1]. Once the compound is introduced via the oral route, it is absorbed in the gastrointestinal tract and undergoes hepatic metabolism including oxidation and hydrolysis, which leads to the production of several metabolites including BPA monosulfate, BPA glucuronide, and BPA disulfate [8]. These metabolites then undergo conjugation and can be excreted in the urine and feces [1]. The presence of BPA and its metabolites can be measured in bodily fluids, including urine and serum, by using the combined techniques of solid-phase extraction coupled with isotope dilution high-performance liquid chromatography and mass spectrometry [9]. Small studies have estimated the half-life of excretion of urinary BPA to approximate 4–5 h [10]. Subsequent pharmacokinetic analyses suggest that the rate of excretion of BPA is not greatly affected by fasting, implying that either BPA is excreted slowly from the body or there exists other significant areas of exposure beyond dietary routes [9, 10].

Epidemiologic studies performed in multiple countries found widespread exposure to BPA. For example, a study

from Korea published in 2011 showed that 99.8 % of the adult population has detectable urinary BPA. A higher concentration of urinary BPA was found in those who resided in rural areas than urban areas. They did not find evidence of significantly different levels of BPA in the urine based on sex, educational level, income, or body mass index [11]. A study of 1016 residents of Sweden, all 70 years or older, examined the serum for levels of BPA and several phthalate metabolites and again confirmed widespread exposure [12]. In the USA, the National Health and Nutrition Examination Survey (NHANES) study conducted from 2003 to 2004, levels tended to be higher among children and adolescents than adults [13]. A large cross-sectional study analyzed urine samples among 1890 Canadian women in the Maternal-Infant Research on Environmental Chemicals (MIREC) study cohort in their first trimester of pregnancy for the presence of BPA or its metabolite glucuronide of BPA. BPA or its metabolites were detected in up to 95 % of urine samples. The highest concentrations of these compounds were measured in the urine of women who were less than 25 years of age, classified as low socioeconomic status or current smokers [14]. A review of greater than 80 exposure and toxicology studies again confirmed the ubiquitous exposure to BPA as measured by the presence of conjugated BPA in the vast majority of urine samples. In addition, levels of free unconjugated and, therefore, active form of BPA were often detected at levels of nanograms per milliliter in serum samples [9].

Phthalates

Phthalates are synthetic diesters of phthalic acid-dialkyl or alkyl/aryl esters of 1,2-benzenedicarboxylic acid [15]. The chemical structures of each individual phthalate vary, mostly according to their side chains and molecular weight. They can be grouped into two broad categories: low molecular weight and high molecular weight. Low-molecular-weight phthalates include dimethyl phthalate (DMP), diethyl phthalate (DEP), and dibutyl phthalate (DBP). High-molecular-weight phthalates include diethyl hexyl phthalate (DEHP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), and benzyl butyl phthalate (BBzP) [15].

Phthalates are similarly produced in high volumes and are used as plasticizing agents. Low-molecular-weight phthalates are commonly found in cosmetics and personal care products, whereas high-molecular-weight phthalates are mostly associated with plastics, particularly polyvinyl chloride (PVC) containing building materials [16–18]. They serve to increase the stability and flexibility of compounds. Dietary exposures are likely the most common source of exposure, especially to the high-molecular-weight phthalates, and frequently occur due to exposure to food and beverage packaging containing PVC [19, 20, 21]. Inhalation exposure occurs through dust from vinyl flooring, carpet backing, and consumer products such as

fragrances, dryer sheets, air fresheners, and sunscreens [22, 23]. The phthalate most often linked to indoor air and dust is DEHP, followed by BBzP [24]. Exposure through dermal contact also occurs with the use of phthalate-containing personal care products such as sunscreens, lotions, and cosmetics [25•]. Environmental exposures to phthalates are increased further due to the lack of covalent binding of phthalates in compounds; this property allows phthalates to leach out of the products and into the air, food, beverage, or personal care product [26]. Once phthalates enter the body, they are metabolized to their monoester forms through a variety of enzymatic conversions. These monoesters and other metabolites are then excreted in the urine [15]. Phthalates and their metabolites can be measured in the urine through a combination of solid-phase extraction coupled with high-performance liquid chromatography–isotope dilution and tandem spectrometry [20••].

As with BPA, the personal exposure to phthalates appears ubiquitous. According to the CDC's Fourth National Report on Human Exposure to Environmental Chemicals of urine samples from 2636 participants in the NHANES study, there was evidence of phthalate metabolites in the urine of almost all participants <http://www.cdc.gov/exposurereport/pdf/fourthreport.pdf>. A study of 200 women and their newborn infants found evidence of phthalate exposure in cord blood and meconium [27]. A study of exposures in Europe found high levels of phthalate metabolites common to products such as makeup, shampoo, and lotion (including dimethyl phthalate (DMP), DEP, BBzP, DINP, and DIDP) in the urine of women [26]. Our research group at the Columbia Center for Children's Environmental Health (CCCEH) detected levels of phthalates among almost all children. Interestingly, CCCEH found higher levels of urinary phthalate metabolites of BBzP, di-*n*-butyl phthalate (DnBP), DEHP, and DEP among boys when compared to girls, but levels did not differ by age [20••].

Links to Allergy and Asthma

There has been growing interest in the effects of exposure to both BPA and phthalates on the alteration of immune function and the development of allergic diseases and asthma. To begin to clarify the link between the environmental exposure and alteration of immune function, we will first examine mechanistic studies followed by cross-sectional and prospective cohort studies.

In Vitro and Ex Vivo Studies

Bisphenol A

The mechanisms by which BPA predisposes to immune deregulation including allergy have not yet been elucidated; only

scant direct mechanistic links have been detected. For example, two studies examined the ability of BPA to activate proallergic T helper (TH) cytokines. One in vitro study showed that BPA upregulated the TH2 pathway and production of interleukin (IL)-4 [28]. In another in vitro study examining the effect on dendritic cells after exposure to BPA versus 17- β estradiol, both with administration of tumor necrosis factor (TNF) alpha, BPA induced greater production of proallergic TH2 chemokines and cytokines, including CC chemokine ligand (CCL)-1, IL-10, IL-5, and IL-13. The expression of Th2 transcription factor GATA-binding protein 3 (GATA3) also was increased [4].

In vitro studies indicate that BPA acts on the estrogen and androgen receptors [29, 30]. Its activation of estrogen receptors has been well documented in studies that showed effects on gene expression, activation of the nuclear estrogen receptor-dependent signaling pathways, and selective estrogen receptor modulation [31, 32]. As an environmental estrogen, BPA may enhance antigen presentation and induce the degranulation of mast cells [33] or promote dendritic cell maturation [34]. BPA also has aromatase-like activity with the ability to convert testosterone to estrogen and to activate the aryl hydrocarbon receptor involved in synthesis and degradation of steroid hormones [35]. These BPA–estrogen receptor interactions have been proposed as possible explanations underlying some of the epidemiological associations between estrogen activity and asthma. These include studies that have shown a rise in rates and severity in asthma as women enter puberty and into adulthood [33]. The severity of asthma has been linked to changes in estrogen levels during the menstrual cycle with one study indicating that up to 40 % of asthmatic women are experiencing exacerbations during the perimenstrual period [36]. Furthermore, a Danish study showed that ever using exogenous estrogen in the form of hormone replacement therapy was associated with an increased risk of asthma-related hospitalizations (hazard ratio 1.46; 95 % confidence interval (CI) 1.21–1.76) [37]. However, due to the paucity of research in this area, no clear mechanism of action has been defined for BPA that fully explains its ability to alter allergic or other immune functions.

Phthalates

While not fully characterized, there has been more investigation into the cellular mechanisms of phthalate effects on allergy. Diethyl phthalate (DEP) also can induce the production of pro-allergic TH-2 cytokines including IL-4 and TNF- α in human macrophages [38]. When human macrophages are exposed to the diethyl hexyl phthalate (DEHP), the production of non-allergic pro-inflammatory chemokines and cytokines in human macrophages was increased [39]. DEHP can cause mast cell to degranulate and release histamine and beta-hexosaminidase [40].

Animal Models

Bisphenol A

In murine studies of the effect of BPA on the development of allergic airway inflammation, prenatal exposure to BPA (0, 0.5, 5, 50, or 500 μg BPA/kg/day) induced variable effects on allergic lung inflammation for the offspring, depending on route of exposure and sex of the offspring. Evidence of increased allergic airway inflammation in those mice exposed prenatally and throughout life to BPA was not evident [41]. In mice exposed during weaning to BPA (50 ng, 50 μg , or 50 mg of BPA/kg) through the dam's diet, there was evidence of increased systemic inflammatory cytokines in the spleen and serum IgE without increased airway inflammation on bronchoalveolar lavage or histologic sections of lung parenchyma [42].

Effects of BPA on ovalbumin-induced allergic airway inflammation reportedly varied based on timing and duration of exposure. Specifically, mice were exposed to either water containing 5 $\mu\text{g}/\text{ml}$ of BPA or regular water during two distinct time periods—prenatally and perinatally through age 21 days or from birth through age 9 weeks. No significant difference in the development of allergic asthma phenotype was seen in mouse pups exposed to BPA via drinking water in the prenatal and perinatal period. However, mice exposed to BPA from birth through age 9 weeks developed higher levels of airway eosinophils, increased airway hyperreactivity, and increased levels of serum IgE [43]. Paradoxical effects were observed if BPA intake occurred only during the sensitization period [43]. Some of these results are corroborated in another experimental study that found that the mouse pups who displayed the asthma phenotype, defined as presence of airway eosinophilia and airway hyperreactivity, were those that were exposed both during the prenatal and postnatal periods to 10 $\mu\text{g}/\text{ml}$ of BPA in the maternal drinking water. Those only exposed in the postnatal period did not exhibit the asthma phenotype [44•]. Hence, ultimately, environmental exposure to BPA may be linked to the development of airway inflammation and possibly even allergic sensitization; however, the effects of BPA exposure are likely modified by time period and by duration of exposure.

Phthalates

The majority of animal model studies on phthalates have focused on one major phthalate, DEHP, and its metabolites. Multiple studies have suggested DEHP's role as an adjuvant leading to an enhanced allergic responses *in vivo*. In one, DEHP's effect on follicular T cells and the allergic response in mice following exposure to DEHP gavage at doses of 0, 30, 300, and 3000 $\mu\text{g}/\text{kg}$ with ovalbumin (OVA) vs sham sensitization were studied. Those mice exposed to DEHP and OVA

sensitized had increased levels of IgE, IgG1, IL-21, and IL-4, supporting the role of DEHP as an adjuvant [45]. In another, mice sensitized to OVA in the presence or absence of DEHP (30, 300, and 3000 $\mu\text{g}/\text{kg}/\text{day}$) via oral gavage were compared. Those exposed to DEHP + OVA exhibited higher levels of proallergic IgE, IL-4, interferon gamma (IFN- γ), and eosinophilia when compared to those mice exposed to OVA alone ($p < 0.05$) [46]. In experimental studies of the links between perinatal effects of exposure to DEHP and the development of airway inflammation, mice were exposed during gestation and for 21 days in the postnatal period to 2500 ppm DEHP via the diet. Airway inflammation was assessed by measurements of mucus and inducible nitric oxide synthase (iNOS), a marker of airway inflammation. Paradoxically, exposure to DEHP was associated with protection from airway inflammation [47]. Dermal exposure to another phthalate, dibutyl phthalate (DBP), also upregulated TH-2 cytokines via increases in thymic stromal lymphopoietin (TSLP) in lymph node cells [48]. In a model of allergic rhinitis, mice sensitized to OVA with and without DEHP did not differ in levels of neutrophils or eosinophils in the nasal mucosa, but the additional exposure to DEHP did increase the production of IL-13 [49].

Other Animal Models of Immunotoxicity

BPA's adverse immunological effects do not seem limited to asthma or allergic airway inflammation in mice. For example, rats exposed to oral BPA at doses of 0.5, 5, or 50 $\mu\text{g}/\text{kg}/\text{day}$ or vehicle control in the perinatal period from 15th day of gravidity through weaning were assessed for perturbations in the development of oral tolerance. Higher titers of anti-OVA IgG, splenic IFN- γ , and activated CD4⁺CD44^{high}CD62L^{low} T lymphocytes were found in OVA-tolerated and OVA-immunized animals, depending on dose. Following oral challenge with OVA among the tolerized animals, colonic inflammation developed with greater neutrophils and IFN- γ and reduced levels of TGF- β , suggestive of abnormal maturation of gut-associated lymphoid tissue (GALT) [50•]. Similarly, OVA-specific T cell receptor transgenic mice exposed to BPA at doses of 0, 0.1, or 1 ppm during pregnancy and weaning demonstrated altered T regulatory (i.e., forkhead box P3 (Foxp3) activity after OVA was administered to the pups on postnatal days 14, 16, and 18. The pups exposed to BPA in the perinatal period had decreased levels of immunoregulatory CD4⁺CD25⁺Foxp3⁺ T cells with higher titers of OVA-specific IgG1, IgG2a, IFN- γ , and IL-13 compared to non-exposed offspring after induction of oral tolerance ($p < 0.05$ for all outcomes) [51].

DEHP also may exert pro-inflammatory effects through oxidative stress-mediated pathways. Mice were divided into six exposure groups: saline, DEHP at 30 mg/kg body weight/day alone, OVA sensitization and challenge alone, DEHP +

OVA, OVA + vitamin E 30 mg/kg/day, and DHEP + OVA + vitamin E. Those exposed to DEHP with OVA sensitization and challenge produced higher levels of reactive oxygen species (ROS) and malondialdehyde and lower levels of glutathione (all $p < 0.05$), consistent with increased levels of oxidative stress. Those treated with vitamin E in addition to DEHP and OVA developed attenuated oxidative stress responses [52].

Epidemiologic Studies

Earlier clues to the contribution of BPA and phthalate exposure to the development of asthma and allergic disease were first derived from intriguing cross-sectional and case control studies. More recent prospective studies have informed us of many links and identified key deleterious time windows of exposure to chemicals (Table 1).

Bisphenol A

A cross-sectional study of the NHANES data examined the relationship between BPA and lung function among 661 children between the ages of 6–19 years of age. Higher levels of BPA in the urine were associated with a moderate decrease in small airway (average forced expiratory flow in percent during the mid (25–75 %) portion of the forced vital capacity (FVC) (3.7 %, 95 % CI 1.0, 6.5) and lung function (% forced expiratory volume at 1 s (FEV₁)/FVC (0.8 %, 95 % CI 0.1, 1.7) but not fractional exhaled nitric oxide (FeNO) [53]. A second NHANES study from 2003 to 2006 found no association between higher levels of BPA and allergy or allergic rhinitis [54].

Importantly, there are several prospective studies that further defined BPA's contribution to airway disease. A cohort study of 375 pregnant women during the third trimester and their children at ages 3, 5, and 7 examined effects of BPA measured in spot urine samples on the development of asthma. Paradoxically, a higher prenatal measure of BPA was related to a reduced report of wheeze at 5 years. As predicted, higher postnatal measures of BPA at age 3 were associated with more frequent wheeze at ages 5 and 6 (odds ratio (OR) 0.7; 95 % CI 0.5–0.9; $p = 0.02$). The detection of higher levels of urinary BPA at the age of 7 was associated with increased risk of wheeze at the age of 7 (OR 1.4; 95 % CI 1.0–1.9; $p = 0.04$). These results support that continued or postnatal exposure to BPA increased the likelihood of developing wheeze [55•].

Similarly, among a second cohort study of 657 pregnant women, prenatal BPA exposure was determined by spot urine BPA concentrations during the first and third trimesters and the development of eczema, allergy, asthma, wheeze, and chest infections including bronchiolitis in the children assessed. Relative risk (RR) of wheeze (RR 1.20; 95 % CI, 1.03–1.40; $p = 0.02$), chest infection (RR 1.15; 95 % CI 1.00–1.32; $p = 0.05$), and development of bronchitis (RR 1.18; 95 % CI 1.01–1.37; $p = 0.04$) increased with every doubling in the concentration of urinary BPA for all age groups. The risk of asthma at age 7 was increased with increased levels or prenatal BPA [56]. A cohort of 398 mothers and children compared urinary BPA levels collected serially during the first and third trimesters, and children were assessed for the presence of wheeze via questionnaire every 6 months for 3 years. As found in previous studies, BPA was present in >99 % of maternal urine samples. Mothers with urine BPA concentrations greater than the median had children who were more likely to report wheeze at 6 months of age (adjusted OR 2.3; 95 % CI

Table 1 BPA and phthalates on asthma-related outcomes: human cohort studies

Number of participants	Study design	Measure(s)	Timing	Outcome(s)	Citation
1890	Cross-sectional	Urinary BPA	First trimester of pregnancy	Differences by age, socioeconomic status, and smoking	Arbuckle [14]
661	Cross-sectional	Urinary BPA	Children 16–19 years	Decreased lung function, no difference in FeNO	Spanier [53]
375	Prospective	Urinary BPA	Third trimester of pregnancy; children 3, 5, 7 years	Prenatal BPA inversely associated with wheeze at age 3, childhood BPA positively with wheeze	Donohue [54]
657	Prospective	Urinary BPA	First and third trimesters of pregnancy	Wheeze, asthma, respiratory infections	Gascon [56]
398	Prospective	Urinary BPA	Second and third trimesters of pregnancy	Wheeze at 6 months	Spanier [57]
405	Cross-sectional	BBzP and DEHP in house dust	Children 3–8 years	BBzP, PVC flooring associated with allergy. DEHP with asthma	Bornehag [58]
184	Case control	DEHP in house dust	Children 2, 3, 5, and 7 years	Allergy	Kolarik [59]
2325	Cross-sectional	Urinary phthalates	Children over 6 years, adults	MBzP, DEHP associated with allergy in adults, not children.	Hoppin [60]
244	Prospective	Prenatal urinary phthalates	Third trimester of pregnancy, children 3, 5, 7 years	Asthma	Whyatt [20•]

1.3, 4.1), but not at age 3 years. A closer analysis of the data found that the higher urine concentrations of BPA at 16-week gestation, but not 26 weeks, were associated with development of wheeze (adjusted OR 1.2; 95 % CI 1.0, 1.5) [57].

Phthalates

A cohort of children in Sweden (198 children with persistent allergic symptoms and 202 controls) was studied for links between exposure to phthalates, including BBzP and DEHP as measured in house dust and the development of allergy and asthma. Data were collected regarding the type of flooring material present in the children's homes, specifically PVC containing versus wood flooring. Higher levels of BBzP were measured in the house dust of allergic cases and among those with the diagnosis of rhinitis ($p=0.001$) and eczema ($p=0.001$). A higher concentration of DEHP in the dust was associated with diagnosis of asthma ($p=0.022$). Not surprisingly, the presence of PVC flooring in the home also was associated with the diagnosis of eczema ($p=0.001$), rhinitis ($p=0.001$), and asthma ($p=0.022$) [58]. A similar case-control study in Bulgaria studied 102 children with wheeze, eczema, or rhinitis in the last year and 82 healthy controls all aged 2–7 years. Dust was collected from their homes and assessed for levels of phthalates including DMP, DEP, di-*n*-butyl phthalate (DnBP), BBzP, DEHP, and di-*n*-octyl phthalate (DnOP). Higher concentrations of DEHP were found in the house dust of allergic cases than controls (1.24 vs. 0.86 mg/g dust). The level of DEHP was related to episodes of wheeze within the last 12 months, and the analysis suggested that there is a dose-response relationship with DEHP exposure [59].

The data from the NHANES study from 2005 to 2006 were examined for the association between phthalates and allergic symptoms including asthma, wheeze, allergy, rhinitis, and hay fever among both adult and pediatric (>6 years) populations. In the adult population, mono benzyl phthalate (MBzP) levels were associated with current asthma, wheeze, hay fever, and allergic rhinitis (OR 1.01–1.78). Inverse or insignificant associations were detected among the children [60]. Within the Columbia Center for Children's Environmental Health (CCCEH) urban birth cohort, the relationship between levels of phthalate metabolites in the urine of 244 children aged 4–9 years and the association with airway inflammation as measured by the fractional excretion of nitric oxide (FeNO) were assessed. Metabolites of DEP and BBzP were associated with an increase in airway inflammation as measured by levels of FeNO. DEP increased FeNO by 6.6 % (95 % CI 0.5–13.1 %), and BBzP increased FeNO by 8.7 % (95 % CI 1.9–16.0 %). Among the children who had reported wheeze during the study period, the association between BBzP and FeNO was stronger ($p=0.016$). Levels of urinary phthalate metabolites

were not associated with levels of IgE, suggestive of a non-atopic mechanism [61].

In an attempt to examine some of the other mechanisms by which phthalates may induce immunotoxicity, the association between phthalates and the levels of oxidative stress in pregnant women was examined in a nested case control study of 130 preterm births with 352 controls delivering in Boston, MA. Urine samples were collected at least four times during pregnancy, and levels of phthalate metabolites and markers of oxidative stress (8-hydroxydeoxyguanosine (OHdG) and 8-isoprostane) were measured. Those with increased levels of phthalates also had higher urinary makers of oxidative stress ($p=0.001$) [62]. Similarly, a prospective cohort study by some of the same investigators assessed 139 pregnant women in Puerto Rico with repeat measures during pregnancy of phthalate urinary metabolites, plasma biomarkers of inflammation, and urinary biomarkers of oxidative stress (OHdG and 8-isoprostane). All of the phthalate metabolites were associated with the biomarkers of oxidative stress, but the larger percent increases were for associations of isoprostane and interquartile range increase in urinary MBP ($\Delta=49.7$, 95 % CI=32.0–69.8) and monoisobutyl phthalate (MiBP) ($\Delta=48.8$, 95 % CI 30.4–69.8) concentrations. Few significant findings with high-molecular-weight, but not low-molecular-weight, metabolites and TNF- α , C-reactive protein, IL-1 β , IL-6, and IL-10 were apparent [63].

There are several prospective studies that furthered our knowledge on phthalates and allergy and airway disease. In one, the risk of prenatal exposure to phthalates was examined for the development of respiratory tract infections, allergy, or asthma by the age of 7. Higher levels of DEHP metabolites were associated with the development of chest infections (RR 1.15, 95 % CI, 0.97–1.35; $p=0.11$), bronchitis (RR 1.20; 95 % CI 1.01–1.43; $p=0.04$), and wheeze (RR 1.25; 95 % CI, 1.04–1.50, $p=0.02$). The risk of developing asthma by age 7 was associated with increased levels of MBzP and DEHP metabolites. MBzP was associated with an increase risk of wheeze (RR, 1.15; 95 % CI, 1.00–1.33; $p=0.05$) [56]. The Dampness in Buildings and Health study conducted in Sweden sought to determine if children exposed to phthalates through PVC flooring were more likely to develop asthma, rhinitis, or allergies. At the start of the study, they queried all children aged 1–6 years in the study area regarding baseline characteristics and qualities of the homes, including the presence of PVC flooring. Over the next 5 years, children were assessed for the development of asthma, rhinitis, or eczema via questionnaire. An association was found between the diagnosis of asthma and the presence of PVC flooring in both the child's bedroom (adjusted OR 1.52; 95 % CI 0.99–2.35) and the parents' bedroom (adjusted OR 1.46; 95 % CI 0.96–2.23). There was also a positive correlation with the number of rooms in the home containing PVC flooring and the incidence of asthma [64]. A second study continued to follow the children for an additional

5 years resulting in 10 years of prospective data. The presence of PVC flooring in the child's bedroom again was associated with the development of asthma in the following 5–10 years (OR 1.49; 95 % CI 0.92–2.42). Interestingly, the strongest association with the development of childhood asthma was the presence of the PVC flooring in the parents' bedroom (OR 1.75; 95 % CI 1.08–2.83), implying that prenatal exposure to phthalates may be associated with delayed detrimental consequences [65].

Our group at CCCEH looked for a link between prenatal exposure to BBzP and the development of eczema. Levels of the main BBzP metabolite, MBzP, were measured in spot urine samples from women in their third trimester of pregnancy. Ubiquitous exposure was again confirmed in this population as MBzP was found in >99 % of urine samples. Increased levels of maternal urinary MBzP were associated with the early onset of eczema (RR=1.52; 95 % CI 1.21–1.91, $p=0.0003$), but not levels of immunoglobulin E [66]. Furthermore, CCCEH examined associations between asthma and phthalates BBzP, DnBP, DEHP, and DEP at age 5–11 years. An association was found between prenatal urinary levels of BBzP and DEP metabolites with the development of asthma-like symptoms and with the diagnosis of asthma during childhood. Notably, the risk of asthma was greater than 70 % higher for the children of mothers who were found to have urinary concentrations of BBzP and DnBP in the third vs. first tertiles [20••].

Conclusions

In the past decade, researchers begun to examine the relationships between common chemical exposures, including BPA and phthalates, and their links to the development of allergy, asthma, and immune dysfunction. It is clear from multiple epidemiologic studies that human exposure to these chemicals is ubiquitous due to their use in a wide range of consumer products, food production, and building materials. The attempts at elucidating the mechanisms by which these chemicals are potentially immune modifying have been sparse, and their results are fairly inconclusive. While the biochemical effects of phthalates have been studied more extensively when compared to BPA, no clear consensus has been made about the underlying mechanisms of allergy and asthma, although DEHP has been studied more extensively in mouse models and most studies do seem to support some role as an adjuvant.

The studies performed in human subjects draw no clear conclusion about the roles that BPA and phthalates play in the rising incidence of allergy and asthma, but they appear to substantiate a link between these chemical exposures and asthma outcomes. Several studies found that increased exposure to BPA was associated with the development of wheeze

or atopy. They also suggest that the timing and duration of exposure to BPA alter the clinical phenotype. Many of the studies are limited by the analysis of spot urine samples and use of self-reported questionnaires to determine the development of allergy, asthma, wheeze, or eczema. Many of the population-based human studies confirm the relationship with phthalates, specifically DEHP, with the increased risk of developing wheeze, asthma, and allergy. The associations between other phthalates and allergy are less clear. The most vulnerable time for exposure to these chemicals also has not yet been determined, although the prenatal period seems to be especially important.

Future research should focus on defining the mechanism of action of these chemicals and the dose at which these effects occur. It will be imperative to discern the key time period for exposure to these chemicals, as well as characterize the most susceptible populations in which immune changes take place. Ultimately, if the research continues to support the existence of a relationship between these chemicals and immune deregulation, it will be necessary to determine methods to limit further exposure to these chemicals.

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Compliance with Ethics Guidelines

Conflict of Interest Lacey Robinson and Rachel Miller declare that they have no conflict of interest.

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- Of importance
- Of major importance

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