Phthalates, Pesticides, and Bisphenol-A Exposure and the Development of Nonoccupational Asthma and Allergies: How Valid Are the Links?

Eun Soo Kwak,[1] Allan Just,[2] Robin Whyatt,[2] and Rachel L. Miller[1,2]*

[1] *Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University College of Physicians and Surgeons, USA*

[2] *Mailman School of Public Health, Columbia University*

Abstract: Phthalates, pesticides, and bisphenol-A (BPA) are three groups of chemicals, implicated in endocrine disruption and commonly found in the local environment, that have been implicated in the pathogenesis of asthma and allergies [1-3]. Multiple observational studies have demonstrated an association between exposure to phthalates and the development of asthma and allergies in humans. Associations with exposure to pesticides and BPA and the development of respiratory disease are less clear. However, recent evidence suggests that prenatal or early postnatal exposure to BPA may be deleterious to the developing immune system. Future cohort-driven epidemiological or translational research should focus on determining whether these ubiquitous chemicals contribute to the development of asthma and allergies in humans, and attempt to establish the routes and mechanisms by which they operate. Determining dose-response relationships will be important to establishing safe levels of these chemicals in the environment and in consumer products. Attempts to reduce exposures to chemicals such as phthalates, pesticides, and BPA may have environmental repercussions as well as public health impact for the developing child.

INTRODUCTION

The rise in asthma prevalence worldwide approximately parallels the rise in common use of several chemicals [4]. While asthma is a complex and heterogeneous disease associated with the inheritance of a genetic predisposition and exposure to many environmental agents, three groups of chemicals, associated with endocrine disruption and commonly found in the local environment, have been implicated recently in its pathogenesis. In this review, conducted through searches and study of recent literature listed in PubMed (www.PubMed.gov), we will discuss accumulating evidence supporting the associations between exposure to phthalates, pesticides, and bisphenol-A (BPA) and the development of asthma and allergies.

PHTHALATES

Phthalates are diesters of benzenedicarboxylic acid and are the most commonly used plasticizers today. Phthalates with the highest production volume are diisononyl phthalate (DiNP), diisodecyl phthalate (DiDP), and di-2-ethyl-hexyl phthalate (DEHP) [2, 5]. Phthalates are used as plasticizers to increase stability and flexibility, to prevent brittleness, as a solvent for fragrances, and as inert ingredients. Phthalates are found in vinyl floor tiles, carpet backing, paints, and wall materials. The majority of DEHP is used as a plasticizer in polyvinyl chloride (PVC) plastics, where it can be 40% of the finished product by weight [6]. Phthalates are commonly found in many other consumer products including shower curtains, adhesives, synthetic leather, toys, cosmetics, and medications. Human exposure to phthalates is evidenced by presence of their metabolites in human urine and other biological samples [7-11]. Diet is believed to be the main source of DEHP exposure in the general population with higher concentrations found in high fat foods like dairy, poultry, and oils [6, 7, 12]. Ingestion of dust and mouthing of toys may be important additional sources of exposure for infants and toddlers [6, 7, 9, 12, 13]. Because they are not covalently bound into plastic when used as plasticizers, phthalates have been found to leach or migrate from PVC-containing items into air, dust, water, soils, and sediment [14].

Multiple studies have examined the association between the presence of PVC in the home flooring and walls, a presumed indicator of phthalate exposure, with the development of asthma and allergies in children. In a Finnish population-based cross-sectional study of 2,568 children 1-7 years of age, the risks of wheezing, persistent phlegm, weekly nasal congestion and respiratory infections were related to the presence of plastic wall materials (presumably including PVC) at home [15]. In a Norwegian matched case-control study of 251 cases of bronchial obstruction and 251 controls, Jaakkola *et al.* found that the risk of bronchial obstruction was greater in the presence of known PVC in the floors [16]. Also, in a Swedish cross-sectional study of 10,851 children, the combination of water leakage and presence of PVC flooring was a strong determinant of doctor-diagnosed asthma and rhinitis compared with those children without leakage and PVC flooring [17]. In their follow-up study of cohort participants recruited 1.5 years later, 198 subjects with persistent allergic symptoms present both at baseline and on follow-up, as well as 202 controls, underwent medical examination and measurement of home dust concentrations of six phthalates (diethyl phthalate (DEP), diisobutyl phthalate (DIBP), di-n-butyl phthalate (DnBP), n-butyl benzyl phthalate (BBzP), diethyl phthalate (DEHP), and diisononyl phthalate (DINP)). Subjects with persistent allergic

*Address correspondence to this author at PH8 E, 610 W. 168th St, New York, NY, 10032, USA; Tel: 212-305-7759; Fax: 212-305-2277; E-mail: rlm14@columbia.edu

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symptoms were more likely to have PVC flooring in the bedroom. Importantly, the median house dust concentrations of BBzP were higher in the bedrooms of subjects with rhinitis and eczema than in those of controls, and the median level of DEHP was greater among those with reports of physician diagnosis of asthma [18]. This study design was replicated in Bulgaria in 2004-2005 with 102 cases and 82 controls with higher DEHP in house dust from cases and a dose-response increase in the odds of being a case or reporting wheeze in the previous 12 months with increasing quartile of DEHP. In Bulgaria, BBzP levels were non-significantly higher in the homes of those reporting wheeze or eczema [19].

Toxicology studies, conducted both *in vitro* and *in vivo* animal models, have proposed various mechanisms by which phthalates may exert their effect on airway inflammation. For example, Nakamura *et al.* examined the effect of three dialkyl phthalates, di-n-butyl phthalate (DnBP), diisobutyl phthalate (DIBP) and di-2-ethyl-hexyl phthalate (DEHP), on antigen-induced degranulation of rat basophilic leukemia (RBL)-2H3 mast cells. Exposure to 50-500 μm DnBP, 50-500 μm DIBP, and 500 μm DEHP significantly potentiated antigen-induced beta-hexosaminidase release. It was concluded that some dialkyl phthalates increase antigen-induced degranulation in RBL-2H3 cells dependent on the increase of cytosolic calcium ion concentrations [20]. Glue *et al.*, in one of the first studies to test potential proallergic adjuvant effects associated with phthalate exposure, found that incubation of the monocytic THP-1 cell line or peripheral blood mononuclear cells (PBMCs) with monophthalates induced virtually no changes in cytokine expression. However, *ex vivo* incubation of PBMCs collected from allergic individuals with mono-n-butyl phthalate (MnBP) tended to increase the level of interleukin [IL]-4 production [21]. In a subsequent study by the same group, rapid histamine release occurred when human PBMCs were incubated with DEHP or mono-(2-ethylhexyl) phthalate (MEHP), then stimulated with anti-immunoglobulin (Ig) E, N-formyl-methionyl-leucyl-phenylalanine (fMLP), calcium ionophore, or cat hair allergen extract. Exposure to the 8-carbon phthalates (DEHP, MEHP, MOP, and DOP) caused the strongest histamine release, whereas incubation with 4-, 9-, or 10-carbon phthalates (MBuP, DBuP, MINP, DINP, MIDP, and DIDP) caused no or low induction of histamine [22]. Jepsen *et al.* showed that the extent of adjuvancy provoked by individual phthalates was structure-related. After exposure to monophthalates, concentrations of the proinflammatory cytokines IL-6 and IL-8 were measured in the human epithelial cell line A549. The study demonstrated that some, but not all, monophthalates could induce a concentration-dependent increase in cytokine production. At higher concentrations, all phthalate doses suppressed cytokine production. Monophthalates with fewer than eight carbon atoms in their alkyl side chain were weak cytokine inducers, whereas monophthalates with eight or more carbon atoms in the alkyl side chain were more potent cytokine inducers. Cytokine suppressive effect of the monophthalates also increased with increasing alkyl side chain length [23].

In an early study in rats, Klimisch *et al.* exposed 9-week-old animals to DEHP aerosols 6 hours/day, 5 days/week, for 4 weeks with estimated doses of 230, 11 and 2.3 mg/kg/day for the males, and 360, 18 and 3.6 mg/kg/day for females. A statistically significant increase (16%) in relative lung weights, accompanied by thickening of the alveolar septi, was found in the males exposed to the highest dose (230 mg/kg). All of these effects were reversed 8 weeks after termination of the aerosol [24]. Larsen *et al.* designed a series of studies to investigate whether a panel of monophthalates (i.e. the principal metabolites of phthalates) had adjuvant properties *in vivo* among mice sensitized to ovalbumin (OVA). While some immunosuppression was observed following exposure to high doses of MEHP, mono-n-octyl phthalate, mono-iso-nonyl phthalate and mono-isodecyl phthalate (MOP, MINP and MIDP) significant increases in proallergic IgE and IgG_1 production occurred following exposure to MEHP (10 μg/ml, IgE), MOP (100 μg/ml, and 10 μg/ml, IgG_1) and MINP (100 μg/ml, IgE) [25]. Next, Larsen *et al.* studied the adjuvant effects of di-n-butyl-, di-n-octyl-, di-iso-nonyl- and di-iso-decyl phthalates (2-2000 μg /ml) in a similar mouse model. Phthalates with 8 or 9 carbon atoms in the alkyl side chains induced greater IgE, IgG_1 production compared to phthalates with shorter or longer alkyl side chains [26].

Hansen *et al.* investigated whether exposure to MEHP induced adjuvant effects in a mouse inhalation model following chronic exposure to low dose OVA. Among mice exposed to aerosols of MEHP, OVA-specific IgG_1, but not IgE or $IgG2_a$, production was increased when compared to mice sensitized to OVA with adjuvant $AI(OH)_3$ only. A dose-dependent increase in eosinophils and lymphocytes also was observed in bronchoalveolar lavage fluid. *Ex vivo* cytokine secretion by cultures of draining lymph nodes also suggested a proallergic T helper (Th) 2 profile following exposure to MEHP [27].

Despite studies that have suggested an association between phthalate exposure and the development of asthma and allergy, one animal model showed a lack of such a relationship. Topical administration of undiluted DEHP, DINP, n-butyl benzyl phthalate (BBzP) and di-isohexyl phthalate (DIHP) to the flanks of mice (50 μL/flank) in the absence of allergen exposure, followed by low dose topical challenge to the ear (25 μL/ear) one week later, did not affect the levels of proallergic cytokine or IgE production [28].

Interestingly, a recent study examined the effect of maternal exposure to DEHP during fetal and/or neonatal periods on subsequent dust mite allergen-induced atopic dermatitis in the offspring. DEHP was administered intraperitoneally at a weekly dose (0.8- 100 μg) per dam during pregnancy and/or lactation. Eight-week-old male offspring were challenged with intradermal injection of mite allergen into their ears. Maternal exposure to DEHP (100 μg) during lactation periods, but not during fetal periods, augmented the development of ear thickening and atopic dermatitis-like skin lesions at the site of allergen injection. Histological evaluation of the tissue showed greater infiltration of eosinophils, mast cell degranulation, and protein expression of eotaxin, consistent with DEHP-induced Th2-dominant allergic dermatitic responses. These effects were not replicated in female offspring, suggesting hormone-mediated processes in the observed phthalate-induced early postnatal effects on allergic immune responses [29].

PESTICIDES

Worldwide there continues to be widespread use of pesticides and herbicides in agriculture, as well as residential pesticide use. While it has been evident for a long time that occupational exposure to pesticides is associated with wheeze and other respiratory symptoms in agricultural workers [1, 30, 31], its association with similar symptoms among nonoccupationally exposed individuals, including children, has gained more recent attention.

For example, Salameh conducted a cross-sectional study on 4000 children from a randomly selected sample of 18 Lebanese public schools assessing the association of exposure to pesticides and reported chronic respiratory symptoms. Using questionnaire data, approximately 12% of children were reported to have a chronic respiratory disease, defined as recurrent cough, expectoration, wheezing with or without dyspnea. Exposure to pesticides was divided into residential, para-occupational and domestic. Residential exposure was characterized by residing in the proximity of a treated field. Domestic exposure was defined as any domestic use by a household member or gardener. Para-occupational exposure was defined as occupational use of pesticides by one or the household members. After controlling for exposure to environmental tobacco smoke in the home, any (residential, domestic or paraoccupational) exposure to pesticides was associated with doctor-diagnosed asthma, chronic cough, chronic phlegm, recurrent wheezing, and ever wheezing [32].

Salam *et al.* conducted a retrospective, prevalence case-control study nested within the Children's Health Study [5] in order to test the hypothesis that environmental exposures in early childhood are associated with increased occurrences of early transient wheezing and/or early-onset persistent asthma. Of 4,244 children who were between 8 and 18 years old at the time of enrollment, 338 children with asthma before 5 years of age, and 570 non-asthmatic controls were matched for age, sex, community of residence and in utero exposure to maternal smoking. Telephone interviews were conducted with mothers to collect additional exposure and asthma histories. Reported exposure to wood or oil smoke, soot, exhaust, dust, herbicides and pesticides during the first year of life was significantly associated with the development of asthma by 5 years of age [5]. However, O'Sullivan *et al.* demonstrated that during the 1999 eradication program of the mosquito vector for West Nile virus in New York City, the spraying of insecticides (malathion, resmethrin) was not associated with an increased rate of emergency room visits or hospitalizations for asthma [33].

Multiple mechanisms have been proposed to explain the effects of exposure to pesticides and the development of asthma or allergy development. Most pesticides are small molecules and can exacerbate asthma and atopic dermatitis symptoms by Type-I and –IV hypersensitivity mechanisms [34]. Exposure to organophosphate and carbamate compounds may trigger respiratory symptoms through cholinesterase inhibition that may promote bronchoconstriction [1]. Fryer *et al.* developed a model of organophosphate-induced airway hyperreactivity in guinea pigs, which suggested that organophosphate-induced airway hyperreactivity results from effects of autoinhibitory M2 muscarinic receptors on the parasympathetic nerves in the lung, not from acetylcholinesterase inhibition or dysfunction of M3 muscarinic receptors in airway smooth muscle [35].

BISPHENOL-A

BPA is used in lacquers to coat food cans and water pipes, and it is also found in dental sealants and composites. Like phthalates, the main source of exposure is believed to be dietary but is not yet well understood. The use of drinking containers made with polycarbonate plastics has been associated with higher exposure [36, 37]. BPA is used in the manufacture of epoxy, polycarbonate plastics, vinyl and unsaturated polyester resins. It also has been used as an antioxidant, fungicide, and antimicrobial in cosmetics. More than a dozen studies using a variety of different analytical techniques have measured free, unconjugated BPA concentrations in human serum at levels ranging from 0.2-20 ng/ml serum [38].

BPA has been measured in human urine from several populations around the world, and the relatively high levels of BPA in the serum of pregnant women, umbilical cord blood, and fetal plasma indicate that BPA crosses the maternal-fetal barrier [39]. In fact, some of the highest levels of BPA reported in human tissue (8.3 ng/ml) occur in amniotic fluid between weeks 15-18 of pregnancy [40]. The latter finding is particularly concerning in light of studies demonstrating that maternal-fetal transmission of BPA, even in small doses, is especially deleterious. For example, Maffini *et al.* reported that perinatal exposure to BPA in mice resulted in morphological and functional alterations of the male and female genital tract and mammary glands that may predispose the tissue to earlier onset of disease, reduced fertility and mammary and prostate cancer [3]. The effects of postnatal exposure to BPA also are concerning. For example, Vandenberg *et al.* showed that in CD-1 mice exposed to BPA during gestation and lactation (starting gestation day 8 and through postpartum day 16 via osmotic pump at constant rate 0.25 μl/h at 0, 0.25, 2.5 or 25 μg BPA/kg/day) demonstrated altered mammary phenotypes including appearance of alveolar buds and intraductal hyperplasia [41].

In comparison to phthalates and pesticides, there are fewer direct studies demonstrating the associations between human BPA exposure and development of asthma or allergy. However, many studies are suggestive of possible links. BPA exposure appears to influence multiple proinflammatory arms of the immune system. For example, Lee *et al.* demonstrated *in vitro* stimulation of keyhole limpet haemocyanin-primed CD4+ T cells with BPA significantly enhanced proallergic IL-4 production in a concentration-dependent manner in mice. Both IL-4 and antigen-specific IgE levels were associated with stimulation of Ca2+/calcineurin-dependent NF-AT activation [42]. Similarly, Tian *et al.* demonstrated that *ex vivo* exposure to BPA resulted in increased production of IL-4 in Th2-dominant mesenteric lymph node cells in mice [43].

Another theme that is becoming evident from the growing literature is that *early* exposure to BPA is particularly associated with heighted inflammation. For example, prenatal [44] and early postnatal [45] exposure of mice induced greater Th2 polarization (ie greater IL-4, reduced interferon (IFN)-γ). Another important finding in the first paper is that

prenatal, more so than during adulthood, exposure to BPA was associated with reduced percentages of T regulatory CD4+CD25+ cells [44], a phenotype associated with atopy [46-48]. Further, the association between prenatal BPA exposure and reduction of T regulatory cells was found in a related mouse model of oral tolerance and food allergies [49].

However, opposite effects may be observed with low doses of BPA, perhaps related to mouse strain or age. For example, BPA exposure of C57BL/6 strain of mice at age 5 weeks was associated with significant reductions in the Th1 IFN-γ production and ConA-stimulated interleukin-10 production [45].

CONCLUSION

In summary, multiple observational studies have demonstrated an association between exposure to phthalates and the development of asthma and allergies in humans. *In vitro* and *in vivo* animal models with different modes of exposure to phthalates support these findings, and provide data suggesting that the association may involve upregulation of allergic immune responses. Associations with exposure to pesticides and the development of respiratory disease, particularly in the pediatric population, are less clear. In particular, there is a lack of prospective studies that focus solely on measured individual pesticides and their role in nonoccupational asthma and allergy development. There is also a dearth of toxicological studies demonstrating the mechanisms by which pesticides exert their effects on the human body. Despite recent evidence suggesting that prenatal or early postnatal exposure to BPA may be deleterious to the developing immune system, even at very low doses, its contribution to asthma pathogenesis, if any, still needs to be elucidated. In animal studies, the doses and blood levels of agents used may not be comparable to actual levels of human exposure, thus translation of results to date to human clinical effects need to be conducted with caution. Currently, there is a lack of studies that utilize biomarkers, such as urinary metabolites, to assess human exposure to these chemicals, independently or in combination.

Even though the three chemicals reviewed in this paper differ in their composition, sources of exposure, and strength of the health effects research, several common themes are apparent. The first is that these chemical exposures are common and the dose level of concern is not known. The second is that prenatal exposure may be a source of particular concern because of potential greater susceptibility of the fetus or because of complex dose response relationships that are not well-understood. The third is that the adverse health effects of these common exposures, especially in regards to asthma and allergies, have not been sufficiently studied.

A key research question is whether or not these ubiquitous chemicals contribute to the development of asthma and allergies in human and, if so, to establish the routes and mechanisms by which they operate. Particular attention should be paid to determining the dose-response relationships and concentrations at which the chemicals become unsafe. Such knowledge could have implications for federal regulation of levels of these chemicals in the environment and in consumer products. A second question is whether early or prenatal exposure to these chemicals is particularly deleterious. Third, how do chemical exposures and genetic makeup interact to heighten susceptibility to chemical exposure on asthma risk?

Cohort-driven epidemiological or translational research, combined with thoughtful experimental design, has great potential to resolve some of these questions. They are particularly relevant topics in this age of "green living," when efforts are being made to minimize the environmental damage caused by common human activities of daily living. Attempts to reduce exposure to chemicals such as phthalates, pesticides, and BPA may not only have environmental repercussions, but may also have public health impact for the developing child.

LIST OF ABBREVIATIONS

BPA	=	bisphenol A
BBzP	=	n-butyl benzyl phthalate
DBuP	=	dibutyl phthalte
DEHP	=	di-2-ethyl-hexyl phthalate
DEP	=	diethyl phthalate
DIBP	=	diisobutyl phthalate
DiDP	=	diisodecyl phthalate
DIHP	=	diisohexyl phthalate
DiNP	=	diisononyl phthalate
DnBP	=	di-n-butyl phthalate
DOP	=	dioctyl phthalate
IL	=	interleukin
Ig	=	immunolgobulin
IFN	=	interferon
MBuP	=	mono-n-butyl phthalate
MEHP	=	mono-(2-ethylhexyl = phthalate
MIDP	=	mono-isodecyl phthalate
MINP	=	mono-iso-nonyl phthalate
MnBP	=	mono-n-butyl phthalate
MOP	=	mono-n-octyl phthalate
OVA	=	ovalbumin
PBMC	=	peripheral blood mononuclear cells
PVC	=	polyvinyl chloride
Th	=	T helper

CONFLICT OF INTEREST

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