



Contents lists available at ScienceDirect



Review

Effects of phthalates on the development and expression of allergic disease and asthma

Michelle L. North, PhD ^{*,†,||}; Tim K. Takaro, MD, MPH, MSc, FACOEM [‡];
Miriam L. Diamond, MSc, MScEng, PhD [§]; and Anne K. Ellis, MD, MSc, FRCPC, FAAAAI ^{*,†,||}

^{*} Department of Biomedical and Molecular Sciences, Queen's University, Kingston, Ontario, Canada

[†] Allergy Research Unit, Kingston General Hospital, Kingston, Ontario, Canada

[‡] Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada

[§] Department of Earth Sciences, University of Toronto, Toronto, Ontario, Canada

^{||} Division of Allergy and Immunology, Department of Medicine, Queen's University, Kingston, Ontario, Canada

ARTICLE INFO

Article history:

Received for publication November 16, 2013.

Received in revised form February 7, 2014.

Accepted for publication March 21, 2014.

ABSTRACT

Objectives: To review recent evidence relating phthalate exposures to allergies and asthma and to provide an overview for clinicians interested in the relevance of environmental health research to allergy and who may encounter patients with concerns about phthalates from media reports.

Data Sources: PubMed, TOXLINE, and Web of Science were searched using the term *phthalate(s)* combined with the keywords *allergy*, *asthma*, *atopy*, and *inflammation*.

Study Selection: Articles were selected based on relevance to the goals of this review. Studies that involved humans were prioritized, including routes and levels of exposure, developmental and early-life exposures, immunotoxicity, and the development of allergic disease.

Results: The general public and those with allergy are exposed to significant levels of phthalates via diet, pharmaceuticals, phthalate-containing products, and ambient indoor environment via air and dust. Intravenous exposures occur through medical equipment. Phthalates are metabolized and excreted quickly in the body with metabolites measured in urine. Phthalates, which are known endocrine disrupting compounds, have been associated with oxidative stress and alterations in cytokine expression. Metabolites in human urine, particularly of the higher-molecular-weight phthalates, have been associated with allergies and asthma in multiple studies.

Conclusion: Despite mounting evidence implicating phthalates, causation of allergic disease by these compounds cannot currently be established. In utero and early-life exposures and possible transgenerational effects are not well understood. However, considering the current evidence, reducing exposures to phthalates by avoiding processed and foods packaged and stored in plastics, personal care products with phthalates, polyvinyl chloride materials indoors, and reducing home dust is advised. Further longitudinal, molecular, and intervention studies are needed to understand the association between phthalates and allergic disease.

© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

North Americans have widespread exposure to phthalates.¹ An increasing literature documents widespread exposure to phthalates and putative links to adverse health effects. Among those potential links is the development and exacerbation of allergic disease.¹ As more evidence comes to light, practicing allergists may find that they are being asked by patients, or parents of patients, whether chemicals such as phthalates cause allergies and how to avoid them. This article provides some background on phthalates and sources of

exposure. We review recent studies that have linked phthalates to allergies and asthma, potential mechanisms of action, and some early research into potential interventions to reduce exposure.

The Structure and Uses of Phthalates

Phthalates are synthetic diesters of phthalic acid that are used in many consumer and building products.^{2,3} Individual phthalate compounds vary in molecular weight and physical-chemical properties according to hydrocarbon chain and branching pattern. The most common phthalates can be loosely grouped into lower molecular weight (dimethyl phthalate [DMP], diethyl phthalate [DEP], and dibutyl phthalate [DBP]), and higher molecular weight (diethyl hexyl phthalate [DEHP], diisononyl phthalate [DINP], diisodecyl phthalate [DIDP], and benzyl butyl phthalate [BBP]). These

Reprints: Anne K. Ellis, MD, MSc, FRCPC, FAAAAI, Division of Allergy & Immunology, Department of Medicine, Queen's University, Doran 1, Kingston General Hospital, 76 Stuart St, Kingston, ON K7L 2V7, Canada; E-mail: ellisa@queensu.ca.

Disclosures: Authors have nothing to disclose.

Table 1
Phthalate diester compounds and corresponding monoester metabolites^a

Phthalate diester	Monoester metabolite
Benzylbutyl phthalate (BzBP)	Monobenzyl phthalate (MBzP)
Dibutyl phthalate (DBP)	Monobutyl phthalate (MBP)
Dicyclohexyl phthalate (DCHP)	Monocyclohexyl phthalate (MCHP)
Diethyl phthalate (DEP)	Monoethyl phthalate (MEP)
Diisobutyl phthalate (DiBP)	Monoisobutyl phthalate (MiBP)
Diisononyl phthalate (DiNP)	Monoisononyl phthalate (MiNP)
Diethyl phthalate (DOP)	Monooctyl phthalate (MOP)
Di-2-ethylhexyl phthalate (DEHP)	Mono-(3-carboxypropyl) phthalate (MCPP)
	Mono-(2-ethylhexyl) phthalate (MEHP)
	Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)
	Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
Dimethyl phthalate (DMP)	Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)
	Monomethyl phthalate (MMP)
Di-isodecyl phthalate (DiDP)	Mono-(carboxynonyl) phthalate (MCNP)

^aAdapted from Health Canada.^{2,5}

2 groups differ in their industrial uses, environmental behavior, and exposure pathways.⁴ Phthalates do not bioaccumulate but are metabolized within a few hours into their corresponding monoesters.^{2,5} Table 1 lists some common phthalate diesters and their corresponding monoester metabolites.

In 2000, the global production of phthalates was 5.2 million metric tons per annum. Their uses include products such as cosmetics, personal care products, adhesives, plastics (including toys), enteric coating of medications, medical equipment, polyvinyl chloride (PVC) building materials (including wall paper and flooring), and other products.^{2,3}

Approximately 90% of phthalates, particularly the higher-molecular-weight compounds, are used as plasticizers (DEHP, DiNP, and DiDP).³ For example, PVC is a rigid polymer unless a plasticizer is added to make it flexible. The lower-molecular-weight phthalates (DMP, DEP, and DBP) are used in solvents, adhesives, waxes, inks, cosmetics, insecticides, and pharmaceuticals.³ Because phthalates are not chemically bonded to the polymers or ingredients to which they are added, they volatilize from the material over time.⁶ Exposure can occur via ingestion of foods that have been in contact with phthalate-containing materials, inhalation, and household dust and via direct contact with a phthalate-containing object (eg, plastic toy). Common products that contain phthalates are detailed in Table 2.

Case Reports

Case reports and series have described occupational asthma related to activities that likely generate phthalate-containing fumes. More than 10 such case reports are summarized in an excellent review by Jaakkola et al,⁷ including cases of verified occupational

asthma caused by hot-wire cutting of PVC, thermoactivated price labels, bottle stoppers, mixtures or resins of phthalates, and fumes from residential fires.⁷ Case reports also indicate that phthalates can cause contact dermatitis, both at occupational exposure levels and in sensitive persons, by something as simple as a PVC wristband.^{8,9} Thus, it is known that phthalate exposure is a real issue and that these chemicals can cause severe allergic reactions that impair quality of life and ability to work. Questions remain regarding the long-term effects of low levels of exposure and allergies or asthma in the general population.

Routes of Exposure

Human exposure to phthalates occurs mainly indoors via a combination of exposure routes discussed below.⁶ These pathways are not mutually exclusive; it is likely that we are exposed through multiple pathways and sources.

Ingestion

Ingestion is an important route of exposure for the general population, including diet, pharmaceuticals, hand-to-mouth transfer of personal care products, and house dust.^{3,10,11} Phthalates have been detected in a wide range of foods, including bottled water, meat, seafood, beverages, grains, and vegetables, with particularly high levels reported in fatty foods.¹² Much of the phthalate content of food likely originates during processing and through migration from plastic packaging and glass jar gaskets.^{12,13} Ample evidence indicates that diet is the major route of exposure to higher-molecular-weight phthalates, such as DEHP and DiNP.¹⁴ Rudel et al¹⁵ convincingly found that exposures to DEHP could be halved by avoiding foods packaged, stored, or heated in plastic.

Dermal

Lower-molecular-weight phthalates are commonly used in cosmetics, personal care products, and other scented products (eg, candles, air fresheners, shampoos). The application of cosmetics and personal care products contributes to dermal exposure at the population scale and can account for much of the interindividual variation seen in phthalate exposure.³ Janjua et al¹⁶ conducted a participant-blinded trial in which participants were given phthalate-free moisturizer and deodorant for a week (control) and a test cream that contained DEP and DBP for another week (treatment). Participants' levels of urinary metabolites significantly increased during the treatment week.¹⁶ Phthalates are also absorbed through the skin from application of perfume and cologne.¹⁴ In a study of 177 pregnant women, Braun et al¹⁷ found that self-reported lotion, cosmetic, and perfume use was associated with phthalate metabolites measured in urine. Thus, although many phthalate exposures are difficult to avoid, reducing the use of scented personal care products is an easy way to reduce exposure.

Table 2
Phthalate diester compounds, CAS numbers, molecular formula, and major uses

Phthalate diesters	CAS No., molecular formula	Common industrial uses and sources
Benzylbutyl phthalate	85-68-7, C ₁₉ H ₂₀ O ₄	PVC, plastics, paints, coatings, adhesives, and printing inks
Dibutyl phthalate	84-74-2, C ₁₆ H ₂₂ O ₄	Polyvinyl emulsions, adhesives, and coatings
Dicyclohexyl phthalate	84-61-7, C ₂₀ H ₂₆ O ₄	Rubbers, resins, polymers, nitrocellulose, polyvinyl acetate, and PVC
Diethyl phthalate	84-66-2, C ₁₂ H ₁₄ O ₄	Plastics, fragrances, cosmetics, and personal care products
Diisobutyl phthalate	84-69-5, C ₁₆ H ₂₂ O ₄	Food, food processing equipment, and food packaging
Diisononyl phthalate	28553-12-0, C ₂₆ H ₄₂ O ₄	PVC, inks, paints, and sealants
Diethyl phthalate	117-81-0, C ₂₄ H ₃₈ O ₄	Polymer manufacturing, PVC, gloves, and flooring
Di-2-ethylhexyl phthalate	117-81-7, C ₂₄ H ₃₈ O ₄	PVC, plastics, medical equipment, and tubing
Dimethyl phthalate	131-11-3, C ₁₀ H ₁₀ O ₄	Solid propellants, plastics, and insect repellents

Abbreviations: CAS, Chemical Abstracts Service; PVC, polyvinyl chloride.

^aAdapted from Health Canada.⁵

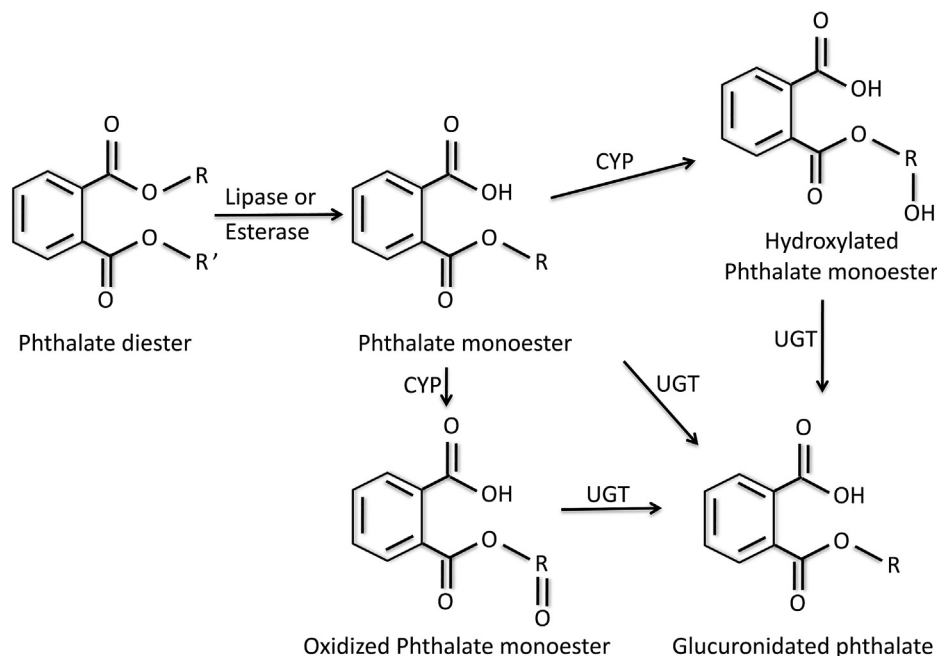


Figure 1. General chemical structure of phthalates and major metabolic pathways. CYP indicates cytochrome P450; UGT, uridine 5'-diphospho-glucuronosyltransferase.

Inhalation

Air concentrations of phthalates are approximately 10 times higher indoors, including cars and workplaces, than outdoors.¹⁸ Children may be at increased risk of inhalational exposure because they inspire more air per kilogram of body weight than adults.³ Some sources of phthalates that have been found to affect indoor air phthalate levels are PVC building materials, furniture, and products, such as scented air fresheners and body fragrances.^{6,14} Evidence indicates that PVC wall and floor coverings release phthalates into indoor air, likely at higher levels if the home is new and/or damp.^{19–21} Because North Americans spend 80% to 90% of their time indoors, the home environment is a significant source of exposure to phthalates.^{10,22} Adibi et al²² found significant correlations between concentrations of DEP, DiBP, and BzBP in indoor air and the corresponding urinary metabolites of 236 pregnant women. A recent study¹⁰ of Danish children confirmed that indoor air meaningfully contributes to total daily intake of phthalates from homes and daycare centers.

House Dust

House dust is known to play a role in phthalate exposure; however, the contribution from this source is unclear and likely varies throughout life. DEHP median concentrations have been found to range from 340 to 858 $\mu\text{g/g}$ of house dust across different countries.^{4,14} Guo et al²³ recently calculated that dust could contribute 10% to 58% of total DEHP exposure to residents in Albany, New York. However, their calculation used US Environmental Protection Agency dust intake levels that contain large uncertainties. Similar to air concentrations, levels of phthalates in settled dust have been associated with the prevalence of PVC building materials indoors.²¹ Little is known about how phthalate levels affect allergic responses to house dust. One group conducted a controlled allergen challenge using dust with high (2090 $\mu\text{g/g}$) and low (410 $\mu\text{g/g}$) levels of DEHP.²⁴ They did not find an effect on symptoms but found that DEHP altered cytokine responses in allergic persons and gene expression responses in both allergic patients and controls.²⁴

Infants and toddlers have the greatest exposure to floor dust, ingest more house dust, and are up to 10 times more vulnerable to such exposure.²⁵ In addition to phthalates, house dust has been suggested to be the main exposure source for infants to allergens, lead, the brominated flame retardants polybrominated diphenyl ethers, pesticides, polycyclic aromatic hydrocarbons, and other environmental chemicals, indicating the need for a deepened understanding of this vehicle for exposure.²⁵ Monitoring their levels in dust and interventions focused on the reduction of dust exposures are areas ripe for future research.

Intravenous

Vulnerable individuals in intensive care can experience acute exposure to phthalates contained in medications, intravenous catheters and blood bags, flexible tubing, and other medical equipment.¹¹ Of note, phthalates may be more effective adjuvants if administered intravenously compared with other routes of exposure.²⁶ Premature infants who spend time in intensive care may be particularly vulnerable to phthalate exposure because of relatively high exposure, their small body size, and the critical developmental window. Calafat et al²⁷ found levels of DEHP metabolites, which were several-fold higher than in the general population in the urine of a group of premature neonates who underwent medical procedures, such as transfusions, intravenous therapy, parenteral nutrition, and dialysis. Green et al²⁸ measured DEHP metabolites in urine from intensive care neonates who were grouped a priori into low, medium, and high exposure groups, based on the medical products used. In a subsequent study,²⁹ 54 infants who were categorized as having high exposure to DEHP-containing medical devices exhibited 13 times higher concentrations of urinary metabolites than the low group. Recently, Su et al³⁰ reported that infants treated with endotracheal and gastric tubes had significantly higher levels of urinary phthalate metabolites than those who were not. Although medical interventions in premature infants and adults may be unavoidable, increased awareness can and is leading to safer alternative materials or strategies to minimize contamination of fluids and air by tubing.

Phthalate Metabolism

A variety of common lipase and esterase enzymes are known to metabolize phthalate diesters through hydrolysis.³¹ The significance of phthalate metabolism is that the monoester metabolites may be as much or more biologically active than the corresponding parent diesters.³ Figure 1 gives the basic chemical structure of phthalate diesters and illustrates the major metabolic pathways. Phthalate monoesters can be hydroxylated or oxidized by cytochrome P450.³¹ Phthalate monoesters and derivatives are also glucuronidated by uridine 5'-diphospho-glucuronosyltransferase, and the glucuronides are not thought to be biologically active.³ Phthalate metabolites are ultimately excreted in the urine and feces.² Phthalate metabolites in urine are often measured to estimate total exposure, rather than the parent compounds, because less contamination during analysis is likely with the metabolites and because of the higher concentration of monoesters vs diesters.^{32,33}

Developmental and Early-Life Exposure

Phthalate exposure occurs throughout the life cycle, from *in utero* to adulthood. Phthalate metabolites have been detected in meconium and cord blood, with cord blood levels being approximately 20% lower than maternal blood, indicating incomplete protection of the fetus by the placenta.³⁴ Zeman et al³⁵ measured elevated levels of phthalates in 279 pregnant women. They found some high concentrations of the primary metabolite of DEHP, which they traced to recent exposures in hospital.

Several studies have suggested an association between prenatal phthalate exposure and adverse effects on development, potentially acting through epigenetic mechanisms. Recently, a mixture of plastic-related chemicals that contained phthalates was found to induce epigenetic transgenerational effects when pregnant rats were exposed.³⁶ Pubertal abnormalities, testis disease, obesity, and ovarian disease were increased in the F3 generation animals, who had not been directly exposed to the chemicals.³⁶ In addition, the sperm epigenome was altered in the F3 generation in specific regions, including 5 genes associated with obesity.³⁶ This study demonstrated that transgenerational epigenetic changes can mediate health status in rodents in the descendants of those exposed to plastic-derived chemicals, including phthalates. Transgenerational effects of phthalates in humans (grandparent exposures that cause grandchild effects) are not well understood or documented at this time because large-scale production of phthalates began only in the 1950s.²⁶ However, it is possible that transgenerational effects could be important as successive generations are exposed. There is a large body of research on the *in utero* endocrine disrupting effects and reproductive toxicity of phthalates.^{11,12} Links to the development of allergies and asthma are only beginning to emerge.

At the infant stage, ingestion likely becomes an important route of exposure. Phthalate metabolites have been found in human breast milk and the urine of infants, including metabolites of DEP, DBP, and DEHP.^{37,38} A Danish-Finnish cohort study reported similar results, as well as detectable levels of monobenzyl phthalate (MBzP) and monoisononyl phthalate (MiNP).³⁹ Mortensen et al¹³ examined both breast milk and infant formula, finding phthalates in both, albeit with varying levels. Early results from 1,539 participants in the Canadian Healthy Infant Longitudinal Development (CHILD) study suggest that despite the presence of phthalates in both breast milk and formula, breastfed infants have lower urinary mono-2-ethylhexyl phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) levels than formula-fed.³⁸ High concentrations of DEHP have also been reported in baby food and traced to plastic tubing used in processing.⁴⁰ These studies

collectively reveal ample opportunities for phthalate exposure in infants in industrialized environments.

In addition to oral exposures from milk, food, and dust, infants may ingest phthalates while mouthing plastic toys. Although recent legislation has restricted the use of particular phthalates in products intended for mouthing (eg, teething rings) and extended to products for use by infants and children, young children may mouth a wide and sometimes surprising array of products that may contain phthalates.³ In addition, dermal exposures are likely to add to the total phthalate burden in children. Sathyanarayana et al⁴¹ found that infant powder and baby lotion significantly elevated urine phthalate metabolite levels in infants younger than 8 months. Thus, infants and children are regularly exposed to phthalates, in some cases at levels that exceed adult exposure, during critical developmental stages, the effects of which are still currently under investigation.

Associations With the Development of Allergy and Asthma

During the prenatal period and in early life, children may be especially sensitive to the immunotoxicity of phthalates. Just et al⁴² found that increases in maternal urinary BBP metabolites during pregnancy were associated with increased odds of eczema presenting before 2 years of age. Interestingly, 0.5% DBP is commonly used as an adjuvant in murine models of atopic dermatitis.⁴³ Shigeno et al⁴³ recently found that DBP administration on the skin is associated with upregulation of T_H2 cytokines and thymic stromal lymphopoietin during the sensitization phase. Exposure studies in rats have indicated that DEHP exposure *in utero* is associated with delayed lung maturation and increased lung interstitial tissue in newborns.⁴⁴ Recently, Vetrano et al⁴⁵ reported the inflammatory effects of phthalates in neutrophils, as well as differences in the ways that adult and umbilical cord blood neutrophils respond. In a 10-year follow-up study in Sweden, Shu et al⁴⁶ reported associations between PVC flooring in the mother's bedroom and development of asthma in her children. Additionally, they reported associations between PVC flooring in the child's bedroom at 1 to 5 years of age and the development of asthma at the 5- and 10-year follow-up time points.⁴⁶ Further longitudinal studies in humans are needed to identify susceptible periods of development.

Data from the National Health and Nutrition Examination Survey (NHANES) in the United States have been instrumental in providing population-level phthalate exposure data and establishing associations between allergic disease and phthalates. Silva et al¹ first examined phthalate urinary metabolites in NHANES participants older than 6 years. They demonstrated that children had significantly higher levels of MBP, MBzP, and MEHP and established key baseline exposure data for the US population.¹ Ferguson et al⁵ then examined urinary phthalate metabolites in relation to biomarkers of inflammation and oxidative stress in 10,031 participants 6 years and older from across the United States. They observed significant positive correlations between MBzP and MiBP and C-reactive protein and between MEHP and γ -glutamyltransferase.⁵ In a follow-up study, the authors also found an association with alkaline phosphatase, ferritin, blood neutrophil count, markers of inflammation, and an inverse association with bilirubin, an antioxidant.⁴⁷ One of the largest studies of allergy and phthalates to date also made use of the NHANES data. Hoppins et al⁴⁸ obtained complete data sets on allergic symptoms, urinary phthalates, and specific IgE from 2,325 participants. They found an association between MBzP and current allergic symptoms in adults but not in children.⁴⁸ However, significant associations in children have been found in a recent cohort study from Taiwan involving 483 mother-infant pairs and longitudinal urinary phthalate measures.⁴⁹ Wang et al⁴⁹ reported

associations between MEHP and serum IgE, as well as MBzP and atopic dermatitis.

Evidence of a link between phthalates and food allergy is limited. However, recently NHANES examined the possible link in 4,979 participants 20 years and older from the 2005–2006 cohort. The authors used a clinical cutoff of 0.35 kU/L of serum IgE antibody, with various thresholds for identification of food allergen sensitization (peanut, 14 kU/L; egg, 7 kU/L; milk, 15 kU/L; and shrimp, 5 kU/L).⁵⁰ They found an association between several phthalate metabolites in urine and shrimp sensitization.⁵⁰ The author suggests a potential relationship between phthalates in shrimp packaging and subsequent sensitization; however, causation cannot be established in this cross-sectional study.

Just as NHANES has pointed to a relationship between phthalates and oxidative stress, other investigations have demonstrated similar associations. Kambia et al.⁵¹ found a significant increase in malondialdehyde, a marker of free radical activity, in infants after undergoing parenteral nutrition compared with before. Oxidative stress markers and phthalate metabolites in urine have recently been linked to decrements in pulmonary function, with effect modifications by polymorphisms in oxidative stress-related genes,⁵² further strengthening the argument that oxidative stress-mediated lung dysfunction may be an important mechanism of phthalate toxicity related to asthma. Indeed, because there is ample evidence that allergic diseases such as asthma are mediated by oxidative stress, more mechanistic studies in this area would be valuable.

Another potentially related mechanism is phthalates acting as adjuvants to enhance the acquisition of allergic sensitization.²⁶ A recent murine allergic rhinitis study demonstrated that administration of DEHP enhances interleukin 13 levels in the nose.⁵³ Although direct evidence of adjuvant activity is lacking at this time, the induction of oxidative stress by phthalates may provide a “danger signal” that is involved in skewing the immune system toward a T_H2 response. Dendritic cells are key antigen-presenting cells that respond to such danger signals. Dendritic cells interact with T cells on encountering an antigen and promote the development of either allergic or tolerogenic responses.⁵⁴ Phthalates have been found to suppress type 1 interferon in human dendritic cells via epigenetic regulation, suggesting they may promote deviation towards the T_H2 response.⁵⁴

Route of exposure may be a key factor determining the health outcomes of phthalate exposure. As discussed above, total exposure to phthalates via ingestion, dermal, and inhalation routes has been found to play a key role in endocrine disruption and reproductive toxicity;^{11,12} however, mounting evidence points to respiratory exposures in the home as an exposure route of interest for allergies and asthma. Case-control studies have revealed that bronchial obstruction was more prevalent in homes with PVC flooring.¹⁸ Further, epidemiologic studies found that the risk of wheezing and asthma were associated with new PVC wall and floor covering, respectively.⁵⁵ A case-control study of children with persistent allergic symptoms revealed higher levels of BzBP in house dust among cases associated with rhinitis and eczema, and DEHP associated with asthma.¹⁹ Hsu et al.⁵⁶ further examined the home environment along with biomonitoring data. They reported that exposure to indoor dustborne BzBP, DBP, and the metabolites MBP and MEHP in urine from children aged 3 to 9 years significantly predicted an increased risk of allergy, asthma, and related symptoms. A cross-sectional study from Norway demonstrated adjusted odds ratios as high as 2.2 for current asthma and biomonitoring measurements of higher-molecular-weight phthalate metabolites.⁵⁷

Studies that link lung inflammation directly to phthalate exposure levels are of critical importance. Fractional exhaled nitric oxide (FeNO) is a common biomarker of pulmonary inflammation. A recent study of 244 New York City children examined the

relationship between urinary phthalate metabolite concentrations and FeNO in 6- to 9-year-old children.⁵⁸ The association between BzBP concentrations and FeNO was stronger in children with parent-reported wheeze.⁵⁸ To examine the hypothesis that inhalational exposures to phthalates are important in driving lung inflammation toward the development or exacerbation of allergic disease, more studies examining lung biomarkers of oxidative stress and inflammation are needed.

Important Considerations

Several factors must be considered when weighing the evidence of an association between allergy and phthalates. Biological markers of phthalate exposure are limited to the period they represent because these markers vary temporally (because of the short half-life of phthalates in the body) and have limited value in evaluating long-term exposure.^{32,33} This makes studies technically challenging and may necessitate multiple samples to ensure the period of interest is adequately represented. Not all studies have repeated measures for the period of interest; thus, the levels of phthalates reported may not necessarily be representative of average exposure.^{32,33} In addition, reverse causation can not be excluded. It is possible that those with allergies, asthma, and atopic dermatitis have higher levels of phthalates because of increased medication or personal care product use.⁵⁷ Interestingly, one of the classic theories surrounding the increased prevalence of allergic disease has been the hygiene hypothesis, which states that increased allergies in Westernized countries may be due to improved cleanliness and thus fewer infections.⁵⁹ Improved cleanliness may also be associated with increased exposure to chemicals in cleaning and home fragrance products. It is not known whether those with allergies and asthma use more personal and home cleaning products than controls and, if this increase does exist, whether it precedes or follows the development of allergy. Further prospective studies will have the opportunity to contribute to our understanding of the complex interactions between genes and environment in allergic disease.

Clinical Relevance

While making every effort not to overstate the likelihood of causation, evidence continues to mount that phthalates, particularly the higher-molecular-weight compounds, may be related to the development of allergic conditions and asthma, along with relevant symptoms of the same. As a preventive measure, clinicians can counsel patients to reduce phthalate exposures. Some simple ways that patients or concerned parents can do this is by reducing their families' consumption of processed foods and foods packaged or stored in plastic and refrain from heating foods in plastic containers. Families can avoid the use of scented personal care products, laundry soap, and phthalate-containing cosmetics. It is not easy to identify which products contain phthalates because legislation does not provide for mandatory labeling. The word “parfum” in a scented product can indicate the presence of a phthalate but this is not failsafe. Parents can also avoid purchasing flexible plastic toys for children that contain phthalates. Legislation in some countries has demanded the removal of some phthalates as a plasticizer in infant and children's products. In terms of the home, PVC flooring, furniture, wallpaper, and other products should be avoided. Manufacturers are using alternative plasticizers in new PVC products; however, the safety of these alternatives has not been well established. It is good practice to minimize dust in the home environment. Phthalates can be detected in products that do not list phthalates on the label.³¹ Many have called for mandatory labeling so that consumers can avoid products that contain phthalates. Interventions such as the Breathe-Easy Home, which included minimization of building materials that release contaminants, including

phthalates, may be possible in the future to reduce exposures in new homes and particularly mobile homes.⁶⁰

Conclusion

Evidence is becoming stronger that allergic conditions and phthalates are linked, particularly the higher-molecular-weight compounds. However, causation of allergic disease cannot be established with the current evidence. Rather than putting the medical and scientific community at ease, we suggest that the current lack of knowledge on the effects of this class of chemicals, to which the general public is highly exposed, is cause for concern. Transgenerational, in utero, and early-life exposures to phthalates are not well understood and have the potential for the greatest harm. Further longitudinal, mechanistic, and intervention studies are needed to understand phthalate toxicity in relation to allergic disease and to identify ways to reduce exposures. Thus, we advocate for a precautionary approach with regard to phthalate exposures wherever possible. Until our understanding improves, the public can take steps to reduce their exposure and improved labeling of consumer products would help achieve this.

References

- [1] Silva MJ, Barr DB, Reidy JA, et al. Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. *Environ Health Perspect.* 2004;112:331–338.
- [2] Canada Health. *Results of the Canadian Health Measures Survey Cycle 2 (CHMS), SECOND Report on Human Biomonitoring of Environmental Chemicals in Canada.* Ottawa, Ontario: Health Canada; April 5, 2013:1–433.
- [3] Takaro TK, Diamond M, Gobas F, Otton V, Shu H. *Critical Review of Phthalates in Canadian Indoor Environments.* Ottawa, Ontario: Health Canada, Safe Environments Program; March 31, 2010:1–128.
- [4] Rudel RA, Camann DE, Spengler JD, Korn LR, Brody JG. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. *Environ Sci Technol.* 2003;37:4543–4553.
- [5] Ferguson KK, Loch-Caruso R, Meeker JD. Urinary phthalate metabolites in relation to biomarkers of inflammation and oxidative stress: NHANES 1999–2006. *Environ Res.* 2011;111:718–726.
- [6] Abb M, Heinrich T, Sorkau E, Lorenz W. Phthalates in house dust. *Environ Int.* 2009;35:965–970.
- [7] Jaakkola JJ, Knight TL. The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. *Environ Health Perspect.* 2008;116:845–853.
- [8] Lensen GJ, Jungbauer FH, Coenraads PJ, Schuttelaar ML. Contact allergy to diisodecyl phthalate. *Contact Dermatitis.* 2012;66:230–231.
- [9] Hills RJ, Iwe FA. Allergic contact dermatitis from diisodecyl phthalate in a polyvinyl chloride identity band. *Contact Dermatitis.* 1993;29:94–95.
- [10] Goto G, Weschler CJ, Langer S, Callesen M, Toftum J, Clausen G. Children's phthalate intakes and resultant cumulative exposures estimated from urine compared with estimates from dust ingestion, inhalation and dermal absorption in their homes and daycare centers. *PLoS One.* 2013;8:e62442.
- [11] Hernandez-Diaz S, Su YC, Mitchell AA, Kelley KE, Calafat AM, Hauser R. Medications as a potential source of exposure to phthalates among women of childbearing age. *Reprod Toxicol.* 2013;37:1–5.
- [12] Kappenstein O, Vieth B, Luch A, Pfaff K. Toxicologically relevant phthalates in food. *EXS.* 2012;101:87–106.
- [13] Mortensen GK, Main KM, Andersson AM, Leffers H, Skakkebaek NE. Determination of phthalate monoesters in human milk, consumer milk, and infant formula by tandem mass spectrometry (LC-MS-MS). *Anal Bioanal Chem.* 2005;382:1084–1092.
- [14] Fromme H, Lahrz T, Piloty M, Gebhart H, Oddoy A, Ruden H. Occurrence of phthalates and musk fragrances in indoor air and dust from apartments and kindergartens in Berlin (Germany). *Indoor Air.* 2004;14:188–195.
- [15] Rudel RA, Gray JM, Engel CL, et al. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary intervention. *Environ Health Perspect.* 2011;119:914–920.
- [16] Janjua NR, Frederiksen H, Skakkebaek NE, Wulf HC, Andersson AM. Urinary excretion of phthalates and paraben after repeated whole-body topical application in humans. *Int J Androl.* 2008;31:118–130.
- [17] Braun JM, Just AC, Williams PL, Smith KW, Calafat AM, Hauser R. Personal care product use and urinary phthalate metabolite and paraben concentrations during pregnancy among women from a fertility clinic [published online October 23, 2013]. *J Expo Sci Environ Epidemiol.* doi:10.1038/jes.2013.69.
- [18] Rudel RA, Perovich LJ. Endocrine disrupting chemicals in indoor and outdoor air. *Atmos Environ.* 2009;43:170–181.
- [19] Bornehag CG, Sundell J, Weschler CJ, et al. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. *Environ Health Perspect.* 2004;112:1393–1397.
- [20] Calafat AM, McKee RH. Integrating biomonitoring exposure data into the risk assessment process: phthalates [diethyl phthalate and di(2-ethylhexyl) phthalate] as a case study. *Environ Health Perspect.* 2006;114:1783–1789.
- [21] Bornehag CG, Lundgren B, Weschler CJ, Sigsgaard T, Hagerhed-Engman L, Sundell J. Phthalates in indoor dust and their association with building characteristics. *Environ Health Perspect.* 2005;113:1399–1404.
- [22] Adibi JJ, Whyatt RM, Williams PL, et al. Characterization of phthalate exposure among pregnant women assessed by repeat air and urine samples. *Environ Health Perspect.* 2008;116:467–473.
- [23] Guo Y, Kannan K. Comparative assessment of human exposure to phthalate esters from house dust in China and the United States. *Environ Sci Technol.* 2011;45:3788–3794.
- [24] Deuschle T, Reiter R, Butte W, Heinzow B, Keck T, Riechelmann H. A controlled challenge study on di(2-ethylhexyl) phthalate (DEHP) in house dust and the immune response in human nasal mucosa of allergic subjects. *Environ Health Perspect.* 2008;116:1487–1493.
- [25] Roberts JW, Wallace LA, Camann DE, et al. Monitoring and reducing exposure of infants to pollutants in house dust. *Rev Environ Contam Toxicol.* 2009;201:1–39.
- [26] Kimber I, Dearman RJ. An assessment of the ability of phthalates to influence immune and allergic responses. *Toxicology.* 2010;271:73–82.
- [27] Calafat AM, Needham LL, Silva MJ, Lambert G. Exposure to di(2-ethylhexyl) phthalate among premature neonates in a neonatal intensive care unit. *Pediatrics.* 2004;113:e429–e434.
- [28] Green R, Hauser R, Calafat AM, et al. Use of di(2-ethylhexyl) phthalate-containing medical products and urinary levels of mono(2-ethylhexyl) phthalate in neonatal intensive care unit infants. *Environ Health Perspect.* 2005;113:1222–1225.
- [29] Weuve J, Sanchez BN, Calafat AM, et al. Exposure to phthalates in neonatal intensive care unit infants: urinary concentrations of monoesters and oxidative metabolites. *Environ Health Perspect.* 2006;114:1424–1431.
- [30] Su PH, Chang YZ, Chang HP, et al. Exposure to di(2-ethylhexyl) phthalate in premature neonates in a neonatal intensive care unit in Taiwan. *Pediatr Crit Care Med.* 2012;13:671–677.
- [31] Dodson RE, Nishioka M, Standley LJ, Perovich LJ, Brody JG, Rudel RA. Endocrine disruptors and asthma-associated chemicals in consumer products. *Environ Health Perspect.* 2012;120:935–943.
- [32] Baird DD, Saldana TM, Nepomnaschy PA, et al. Within-person variability in urinary phthalate metabolite concentrations: measurements from specimens after long-term frozen storage. *J Expo Sci Environ Epidemiol.* 2010;20:169–175.
- [33] Hauser R, Meeker JD, Park S, Silva MJ, Calafat AM. Temporal variability of urinary phthalate metabolite levels in men of reproductive age. *Environ Health Perspect.* 2004;112:1734–1740.
- [34] Li LX, Chen L, Meng XZ, et al. Exposure levels of environmental endocrine disruptors in mother-newborn pairs in China and their placental transfer characteristics. *PLoS One.* 2013;8:e62526.
- [35] Zeman FA, Boudet C, Tack K, et al. Exposure assessment of phthalates in French pregnant women: results of the ELFE pilot study. *Int J Hyg Environ Health.* 2013;216:271–279.
- [36] Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. *PLoS One.* 2013;8:e55387.
- [37] Zhu J, Phillips SP, Feng YL, Yang X. Phthalate esters in human milk: concentration variations over a 6-month postpartum time. *Environ Sci Technol.* 2006;40:5276–5281.
- [38] Shu H, Ryan A, Bornehag C-G, et al. CHILD Environmental Working Group. Phthalate exposures in a Canadian birth cohort at three months of age: the CHILD study. *Allergy Asthma Clin Immunol.* 2014;10(suppl 1):A56.
- [39] Main KM, Mortensen GK, Kaleva MM, et al. Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age. *Environ Health Perspect.* 2006;114:270–276.
- [40] Tsumura Y, Ishimitsu S, Saito I, Sakai H, Kobayashi Y, Tonogai Y. Eleven phthalate esters and di(2-ethylhexyl) adipate in one-week duplicate diet samples obtained from hospitals and their estimated daily intake. *Food Addit Contam.* 2001;18:449–460.
- [41] Sathyanarayana S, Karr CJ, Lozano P, et al. Baby care products: possible sources of infant phthalate exposure. *Pediatrics.* 2008;121:e260–e268.
- [42] Just AC, Whyatt RM, Perzanowski MS, et al. Prenatal exposure to butylbenzyl phthalate and early eczema in an urban cohort. *Environ Health Perspect.* 2012;120:1475–1480.
- [43] Shigeno T, Katakuse M, Fujita T, Mukoyama Y, Watanabe H. Phthalate ester-induced thymic stromal lymphopoietin mediates allergic dermatitis in mice. *Immunology.* 2009;128:e849–e857.
- [44] Chen SQ, Chen JN, Cai XH, et al. Perinatal exposure to di(2-ethylhexyl) phthalate leads to restricted growth and delayed lung maturation in newborn rats. *J Perinat Med.* 2010;38:515–521.
- [45] Vetrano AM, Laskin DL, Archer F, et al. Inflammatory effects of phthalates in neonatal neutrophils. *Pediatr Res.* 2010;68:134–139.
- [46] Shu H, Jonsson BA, Larsson M, Nanberg E, Bornehag CG. PVC flooring at home and development of asthma among young children in Sweden, a 10-year follow-up [published online October 10, 2013]. *Indoor Air.* doi:10.1111/ina.12074.
- [47] Ferguson KK, Loch-Caruso R, Meeker JD. Exploration of oxidative stress and inflammatory markers in relation to urinary phthalate metabolites: NHANES 1999–2006. *Environ Sci Technol.* 2012;46:477–485.

- [48] Hoppin JA, Jaramillo R, London SJ, et al. Phthalate exposure and allergy in the U.S. Population: results from NHANES 2005–2006. *Environ Health Perspect.* 2013;121:1129–1134.
- [49] Wang IJ, Lin CC, Lin YJ, Hsieh WS, Chen PC. Early life phthalate exposure and atopic disorders in children: a prospective birth cohort study. *Environ Int.* 2014;62:48–54.
- [50] Shiue I. Association of urinary arsenic, heavy metal, and phthalate concentrations with food allergy in adults: National Health and Nutrition Examination Survey, 2005–2006. *Ann Allergy Asthma Immunol.* 2013;111:421–423.
- [51] Kambia N, Dine T, Gressier B, et al. Correlation between exposure to phthalates and concentrations of malondialdehyde in infants and children undergoing cyclic parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2011;35:395–401.
- [52] Park HY, Kim JH, Lim YH, Bae S, Hong YC. Influence of genetic polymorphisms on the association between phthalate exposure and pulmonary function in the elderly. *Environ Res.* 2013;122:18–24.
- [53] He M, Inoue K, Yoshida S, et al. Effects of airway exposure to di-(2-ethylhexyl) phthalate on allergic rhinitis. *Immunopharmacol Immunotoxicol.* 2013;35:390–395.
- [54] Kuo CH, Hsieh CC, Kuo HF, et al. Phthalates suppress type I interferon in human plasmacytoid dendritic cells via epigenetic regulation. *Allergy.* 2013;68:870–879.
- [55] Jaakkola JJ, Jeromnimon A, Jaakkola MS. Interior surface materials and asthma in adults: a population-based incident case-control study. *Am J Epidemiol.* 2006;164:742–749.
- [56] Hsu NY, Lee CC, Wang JY, et al. Predicted risk of childhood allergy, asthma, and reported symptoms using measured phthalate exposure in dust and urine. *Indoor Air.* 2012;22:186–199.
- [57] Bertelsen RJ, Carlsen KC, Calafat AM, et al. Urinary biomarkers for phthalates associated with asthma in Norwegian children. *Environ Health Perspect.* 2013;121:251–256.
- [58] Just AC, Whyatt RM, Miller RL, et al. Children's urinary phthalate metabolites and fractional exhaled nitric oxide in an urban cohort. *Am J Respir Crit Care Med.* 2012;186:830–837.
- [59] Strachan DP. Hay fever, hygiene, and household size. *BMJ.* 1989;299:1259–1260.
- [60] Takaro TK, Krieger J, Song L, Sharify D, Beaudet N. The Breathe-Easy Home: the impact of asthma-friendly home construction on clinical outcomes and trigger exposure. *Am J Public Health.* 2011;101:55–62.