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Phthalate Exposure and Children's Health

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Abstract

Purpose of Review—Phthalates are multifunctional chemicals used in personal care products, medications, and plastics. We reviewed the epidemiological literature examining the relationship between early life phthalate exposure and pediatric health outcomes.

Recent Findings—Five studies from Asia, Europe, and the US suggest that childhood exposure to di-2-ethylhexyl phthalate (DEHP) and butylbenzyl phthalate (BBzP) may increase the risk of allergic diseases including asthma and eczema. Six studies from four different prospective cohorts report that gestational BBzP, DEHP, di-butyl phthalate (DBP), and di-ethyl phthalate (DEP) exposures are associated with alterations in infant/toddler physical development as well as parent-reported externalizing, internalizing, and autistic-like child behavior. However, there are inconsistencies related to the specific phthalates and behavioral domains. Two small studies report shorter anogenital distance among male infants with higher gestational phthalate exposure.

Summary—Several epidemiological studies suggest fetal and childhood exposure to some phthalates may perturb normal development, with several studies consistently reporting increased risk of allergic diseases with DEHP and BBzP exposure. While anticipatory guidance is not evidence-based at this time, providers can counsel concerned patients to reduce phthalate exposures in order to protect the developing fetus and child from potential adverse health outcomes.

Keywords

Phthalates; Epidemiology; Children; Endocrine Disruption

Introduction

Ortho-phthalates are synthetic chemical esters of phthalic acid and serve multifunctional roles in a variety of consumer products resulting in ubiquitous daily exposures in adults and children [1–3]. Some phthalates are suspected endocrine disrupting compounds (EDCs),

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Conflicts of Interest
The authors have no conflicts of interest.

with well described anti-androgenic properties in prenatally exposed rats. Phthalates have received both media attention and regulatory scrutiny because of their use in numerous consumer products; measurable exposure in pregnant women, infants, and children; and potential to adversely affect normal human development. This review will summarize the current epidemiological literature on early life phthalate exposure and health outcomes.

Phthalate Metabolism and Exposure

Low molecular weight (LMW) phthalates like di-methyl phthalate (DMP), di-ethyl phthalate (DEP), and di-butyl phthalate (DBP) are used as aerosol delivery agents and emollients and impart flexibility in nail polishes and retain scents in scented products sold in the US and Canada [4–6] (Table 1).

Epidemiological studies have confirmed that the use of certain personal care products is associated with elevated urinary phthalate monoester metabolite concentrations. The use of colognes, perfumes, facial cream, lotion, and cosmetics is associated with elevated levels of DEP and DBP metabolites in adults [22–26]. In a study of infants, Sathyanarayana and colleagues reported elevated levels of several different phthalate metabolites in infants who had been exposed to baby lotion, powder, or shampoo in the last 24 hours [27]. These associations were stronger in infants ≤8 months of age, suggesting that some baby care products may be the primary exposure sources before infants begin to crawl and develop increased hand-to-mouth activities later in infancy.

High molecular weight (HMW) phthalates including di-2-ethylhexyl phthalate (DEHP), butyl benzyl phthalate (BBzP), di-n-octyl phthalate (DnOP), di-isononyl phthalate (DiNP), and di-isodecyl phthalate (DiDP) are commonly used as plasticizers to impart flexibility in hard polyvinyl chloride plastics (Table 1). HMW phthalates are also used in adhesives, some food packaging, rainwear, and other vinyl products. These high molecular weight phthalates are not covalently bound to plastics so they can leach from products over time. The presence and quantity of vinyl flooring may present a source of oral and inhalational exposure to DEHP and BBzP due to their presence in vinyl flooring [28,29]. Plastic materials used in food processing and storage may also increase the phthalate content of some foods and a recent randomized trial suggests that families may be able to reduce their phthalate exposure by eliminating the use of these materials in food preparation [30].

Of specific concern for children with chronic diseases is the use of phthalates in medications, supplements, and polyvinyl chloride medical products/devices. DBP and DEP are used as excipients in some time released medications [31]. A case report and cross-sectional study reported some of the highest recorded urinary DEP and DBP metabolite concentrations among adults using theophylline, mesalamine, omeprazole, and didanosine [32,33]. No studies have evaluated these medications as a source of phthalate exposure in pregnant women, infants, or children. The FDA recently issued non-binding guidance that urges drug manufacturers to remove DBP or DEHP from excipient formulations in medications [34]. The use of DEHP-containing medical devices, including some indwelling endotracheal tubes and umbilical vessel catheters, can result in elevated DEHP exposures in NICU infants [35]. DEHP is also used in many medical devices including intravenous (IV) tubing, IV fluid bags, total parenteral nutrition bags/tubes, and catheters [36–38]. The use of DEHP-containing medical devices can result in acute exposures that exceed the tolerable daily intake after medical interventions like platelet donation [39]. Elevated DEHP exposure may also occur during labor and delivery [40].

In infants, toddlers, children, and adolescents, the sources and routes of phthalate exposure are related to developmental milestones and will be determined by hand-to-mouth activity, mobility, personal care/hygiene practices, diet, and health status throughout development

[41]. This is important to consider when advising parents about potential sources of exposure. In general consumer products and indoor air present the greatest sources of DMP, DEP, BBzP, DiNP, and DiDP; whereas food is the major source of DEHP and possibly DBP. Infants and toddlers have much higher phthalate intakes because of their increased food/water requirements per unit body mass, hand-to-mouth activity, and ventilation rate.

Following intake, phthalates rapidly undergo hydrolysis into their respective monoesters (Table 1). Some phthalates undergo further Phase 1 oxidative metabolism before being glucurondiated or sulfated and finally excreted in the urine [42]. Phthalates do not bioaccumulate and have biological half-lives <24 hours [43,44]. While phthalates can be measured in blood, urine, breast milk, and meconium [45–47], urine is typically used in epidemiological studies since it integrates exposures over the last several hours, is non-invasive to collect, and may reasonably reflect exposures occurring in the last several days or weeks [48– 50].

Infant and Child Health Outcomes

There is concern over the potential for both fetal, infant, and childhood phthalate exposure to disrupt normal growth and development. The toxicity of ortho-phthalates has been studied for almost 40 years in animal studies and several phthalates have anti-androgenic properties in male rats exposed in utero [51]. Gestational phthalate exposure reduces Leydig cell testosterone production by decreasing gene expression in the cholesterol biosynthesis/trafficking and steroidgenic enzymatic pathways. The reduction in fetal testosterone production results in observable abnormalities in the rat including nipple retention, reduced anogenital distance, and genital malformations [52–55]. The fetus is most sensitive to the anti-androgenic effect of phthalates, while the pubertal rat is less sensitive and the adult least sensitive [56]. The action of phthalates may not be solely limited to androgen-sensitive systems and some phthalates may act through the peroxisome proliferator-activated receptor γ (PPAR-γ) [53,57].

Below we describe studies examining the relationship between fetal, infant, and child phthalate exposures with several childhood health outcomes

Gestational Length and Infant Size at Birth

Seven studies have examined the relationship between maternal urinary phthalate metabolite concentrations and duration of gestation or infant anthropometrics. A study of 283 mother-infant pairs reported slightly longer gestational length (~1 day) with increasing urinary DEHP metabolites in a multi-center cohort from the US [58]. In addition, higher DEHP metabolite concentrations were associated with 2-times the odds of delivery after 41 weeks. Another study of 404 New York City mother-infant pairs reported a trend of longer gestation among women with higher DEHP and DEP metabolite concentrations [59]. One nested case-control study of 60 infants (30 preterm) from Mexico City reported 2–3 times the odds of preterm birth among women with higher urinary phthalate metabolite concentrations compared to women with lower concentrations [60]. Another prospective cohort of 289 mothers and infants in New York City reported shortened gestational length (~5 days) among women with the highest urinary DEHP metabolite concentrations [61]. A study of 84 infants reported shorter gestational length among infants with detectable cord blood DEHP metabolite concentrations [62].

Two prospective cohorts from France (n=191) and New York City (n=404) reported null associations between 10 different urinary phthalate metabolites collected from women during pregnancy and infant weight, length, and head circumference at birth [59,63]. A case-

control study reported higher meconium DEHP and DBP metabolites in 88 term low birth weight infants compared to 113 normal birth weight controls from China [45].

In summary, there is inconsistent evidence for an association between phthalate exposure and length of gestation or infant size at birth. Differences in the timing and matrix (e.g., serum vs. urine vs. meconium) of phthalate exposure measurement during pregnancy may contribute to the discrepant results across studies.

Physical Growth

Three cross-sectional studies from the US and Denmark examined the relationship between urinary phthalate metabolite concentrations and anthropometry in school-age and adolescent children. In a nationally representative sample of 6–11 (n=327) and 12–19 (n=682) year old girls in the US, Hatch et al. observed increased BMI among adolescent girls with higher DEP metabolite concentrations [9]. Teitelbaum and colleagues also observed a positive association between DEP metabolites and BMI among 387 New York City children that was comparable in magnitude to Hatch [10]. Boas et al. reported inverse associations between urinary phthalate metabolites and anthropometric measurements in 845 school age children from Denmark [64]. As noted by Hatch et al., the results of studies showing a positive correlation between urinary DEP metabolites and BMI may be due to reverse causality since higher BMI individuals have greater body surface area, making them more likely to use a greater quantity of phthalate-containing personal care products (e.g., lotion) than lower BMI individuals.

Asthma and Allergy

Five studies, three case-control, one prospective, and another cross-sectional examined the relationship between phthalates and respiratory and allergic diseases in children. In a prospective cohort of 407 women-child pairs from New York City, increasing maternal urinary BBzP metabolites during pregnancy were associated with a 50% increased odds of early-onset (defined as presenting ≤ 24 months of age) eczema in children [19]. Three studies (n=400, 184, and 101) using a nested case control design examined the relationship between settled dust phthalate concentrations and childhood asthma, eczema, or rhinitis in children from Bulgaria, Sweden, and Taiwan [17,18,65]. Two of these studies reported higher DEHP dust concentrations in the homes of case children compared to controls [18,65]. Children in the highest quartile of DEHP dust concentrations were 1.4 to 2.7 times as likely to have allergy, asthma, rhinitis, or wheezing symptoms compared to children in the lowest quartile. In addition, two studies observed increased odds of asthma, eczema, or rhinitis among children residing in homes with dust BBzP concentration in the highest quartile compared to those in the lowest quartile [18,66]. A study of 244 New York City children examined the relationship between four urinary phthalate metabolite concentrations and fractional exhaled nitric oxide (FeNO) in 6–9 year old children[67]. After adjustment for confounders and seroatopy, increasing DEP and BBzP metabolite concentrations were associated with 6.6 and 8.7% higher FeNO concentrations, respectively. The association between BBzP concentrations and FeNO was stronger in children with parent-reported wheeze.

There is converging evidence that DEHP and BBzP exposures during childhood may be associated with the development of allergic disease. In animal studies, phthalates act as PPAR α and γ agonists or adjuvants resulting in changes in airway remodeling or allergen response, respectively [68,69]. Longitudinal studies are needed to identify susceptible periods of development and future studies will need to control for other environmental risk factors for asthma that may covary with phthalate exposure.

Neurodevelopment

Ten studies have examined the relationship between phthalate exposures and child neurodevelopment. In a cross-sectional study of 667 school-aged Korean children, Cho et al. reported a 2-point reduction in IQ with higher urinary DEHP and DBP metabolite concentrations; however this association was attenuated to the null after adjustment for maternal IQ [70]. Another cross-sectional study observed elevated urinary DEHP metabolite concentrations in the urine of 48 children with autism spectrum disorders compared to 45 controls [71]. However, this study did not control for potential confounders and assessed exposure concurrently with case diagnosis.

A prospective cohort study of 417 Korean mother-infant pairs reported lower mental and physical developmental scores among infants born to women with higher gestational urinary DEHP and DBP metabolite concentrations, even after controlling for maternal IQ[14]. These findings are consistent with another study of 296 mother-child pairs from New York City that reported reduced physical development at 3 years of age among children born to women with higher urinary DBP metabolite concentrations [61].

Two studies from New York City (n=295) and Cincinnati (n=355) examined the relationship between maternal phthalate exposure during pregnancy and infant behavior using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) and NICU Network Neurobehavioral Scale (NNNS) [72,73]. In the New York City study, maternal urinary phthalate metabolite concentrations were associated with better orientation and motor scores in boys on the BNBAS, but associated with poorer orientation and quality of alertness in girls [72]. In Cincinnati higher DBP metabolite concentrations were associated with improved arousal and regulation, less need for handling, improved movement quality, and more non-optimal reflexes among all infants [73].

Three prospective studies from two US cohorts and one cross-sectional study from Korea examined the relationship between maternal urinary phthalate concentrations during pregnancy and parent- or teacher-reported child behavior. Engel et al. reported more ADHD-like behaviors among 188 4–7 year olds whose mothers had higher urinary DEP and DBP metabolite concentrations during pregnancy [7]. Another study from the same cohort reported more autistic-like behaviors among 7–9 year old children born to women with higher urinary DEP and DBP concentrations [8]. In a group of 277 New York City mother-child pairs, Whyatt et al. reported more internalizing behaviors among 3 year old children born to women with higher urinary DBP and BBzP metabolite concentrations [15]. They also found that children born to women with higher BBzP exposure had 1.3–1.4 times the risk of borderline or clinically significant internalizing behaviors. A study of 261 Korean school children reported more teacher-rated ADHD-like behaviors in children with higher urinary DEHP metabolite concentrations [74].

A study by Swan et al. (n=74) reported less masculine parent-reported play behaviors among boys born to women with higher gestational urinary DEHP and DBP concentrations [13]. These findings are intriguing given these investigator's prior findings of reduced AGD among this same group of boys [12].

While there are a large number of studies suggesting a potential link between gestational/childhood phthalate exposure and neurodevelopment, there are inconsistent phthalate-behavioral domain associations that could be due to the different behavioral/cognitive domains tested at different ages and varied timing of exposure measures across studies.

Genital and Pubertal Development

Two studies of male infants in the US (n=85) and Japan (n=111) observed an inverse association between maternal DEHP metabolite concentrations and anogenital distance (AGD) [12,20], while a smaller study of 65 Taiwanese infants did not observe this relationship [75]. AGD is a marker of fetal testosterone production by the testis and reductions in AGD have been observed in rats prenatally exposed to some phthalates [56].

A large prospective cohort study (n=1,151) examined the relationship between childhood phthalate exposure and pubertal development in girls one year later [76]. The results from this well-powered study reported an increased prevalence of stage 2+ breast/pubic hair development among girls with the highest exposure to LMW phthalates like DEP and DBP compared to those with the lowest exposure (Prevalence Ratio [PR]=1.06). In contrast, girls with the highest exposure to HMW phthalates, including DEHP and BBzP, had a modestly lower prevalence of pubic hair development (PR=0.94) compared to girls with the lowest exposure. A cross-sectional study of 725 Danish girls reported delayed onset of pubic hair development among girls with higher urinary phthalate concentrations, specifically metabolites of DBP and BBzP [16].

The evidence of reduced AGD among male infants in two cohorts is consistent with findings in male rat pups prenatally exposed to phthalates (34). Two studies suggest that childhood exposure some phthalate metabolites may be associated with delayed onset of pubarche. Additional studies examining the impact of phthalate exposure on pubertal development in boys are needed given the anti-androgenic properties of phthalates.

Conclusions and Clinical Recommendations for Providers

The results of several well-designed studies consistently suggest that low-level childhood DEHP and BBzP exposures may increase the risk of allergic diseases. Several studies suggest that gestational phthalate exposure may increase behavioral problems in childhood, but there is an inconsistent pattern related to the specific phthalates and behavioral domains. Consistent with findings in rats, two prospective cohort studies observed decreased AGD in infants with higher gestational phthalate exposure. Two cross-sectional studies observed delayed onset of pubic hair development among girls with higher exposure to some phthalates.

In recent years, there has been substantial media and public attention given to the potential health risks associated with phthalate exposure. These concerns have led to the US Consumer Product Safety Improvement Act (CPSIA) of 2008, which banned the use of BBzP, DEHP, and DBP in children’s toys and child care articles and placed an interim ban on DnOP, DiNP, and DiDP [77]. Despite these measures, childhood phthalate exposure persists, likely due to the ubiquitous use of these chemicals in many consumer products. In addition, these regulations may not protect the developing fetus since they do not reduce phthalate exposures among women of child bearing age.

Currently, no evidence based methods to reduce exposures exist but many scientific and professional organizations have made recommendations to reduce exposure [78]. Healthcare providers can counsel concerned patients to avoid using personal care products that may contain DEP and DBP, particularly scented products like colognes and perfumes. There are no requirements for these products to include phthalates in their ingredient lists, which makes it difficult to reduce exposure by avoiding specific products. In order to decrease exposures to DEHP or BBzP, patients can avoid using vinyl flooring and minimize dusty environments by taking shoes off at the door, keeping windowsills clean, and moping/vacuuming consistently. Avoiding processed foods, foods packaged and stored in plastics,

and using non-plastic cookware and storage materials may decrease DEHP and possibly DBP exposures [30,41]. Medical providers may be able to reduce or eliminate DEHP exposure associated with certain medical procedures by using alternative products (www.sustainablehospitals.org) [79]. Until governmental regulations to limit phthalate exposure are enacted, additional research to identify the primary sources of phthalate exposure, develop interventions to reduce exposures, and understand the health impacts of early life phthalate exposure would provide patients and clinicians with strategies to reduce exposure and assist policy makers in the ongoing risk-assessment process.

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Key Points

- Phthalates are a multifunctional class of chemicals used in polyvinyl chloride plastics, personal care and beauty products, time-release medications, and some plastic medical equipment. Pregnant women and children from industrialized countries are almost universally exposed to multiple phthalates on a daily basis.
- Several studies have reported an increased risk of allergic disease among children with higher childhood phthalate exposure, as well as increased airway inflammation.
- Some human studies suggest that *in utero* phthalate exposure could lead to abnormal genital and behavioral developmental.
- Based on our current understanding, diet and dust are the predominant sources of di-(2-ethylhexyl) phthalate and butylbenzyl phthalate, while cosmetics are the major source of diethyl phthalate.
- Clinicians can counsel patients to reduce phthalate exposure by decreasing consumption of processed/packaged foods, avoiding personal care products that contain phthalates, and minimizing dusty environments.

Table 1

Ortho-phthalates commonly used in consumer products, their, primary metabolites, use in consumer products and reported childhood health effects in epidemiological studies *

Phthalate (Abbreviation)	Metabolites Measured in Epidemiological Studies (Abbreviation) †	Uses in Commerce	Reported Health Effects in Infants/Children †
Dimethyl phthalate (DMP)	Mono-methyl phthalate (MMP)	• Scent retainer in cosmetics and personal care products. • Adhesives.	• Studies report null associations with childhood health outcomes.
Diethyl phthalate (DEP)	Mono-ethyl phthalate (MEP)	• Scent retainer in cosmetics, colognes/ perfumes, and personal care products. • Excipient in pharmaceuticals and supplements.	• Prenatal exposure associated with increased behavior ADHD-like and autistic-like behaviors. [7,8] • Concurrent exposure associated with increased BMI and waist circumference in girls. [9,10] • Concurrent exposure associated with increased FeNO concentrations. [11]
Dibutyl phthalate (DBP)	Mono-butyl phthalate (MBP) Mono-3-carboxy-propyl phthalate (MCPP)	• Scent retainer in cosmetics and personal care products. • Excipient in pharmaceuticals and supplements. • Plasticizer in nail polish and cellulose plastics. • Used in certain adhesives.	• Prenatal exposure associated with decreased AGD in male infants [12] and reductions in masculine play behavior among boys. [13] • Prenatal exposure associated with decreased mental and physical development in 6 month olds [14], decreased physical development in 3 year olds [15], and increased internalizing behaviors in 3 year olds. [15] Concurrent

Phthalate (Abbreviation)	Metabolites Measured in Epidemiological Studies (Abbreviation) †	Uses in Commerce	Reported Health Effects in Infants/Children†
			exposure associated with delayed pubarche in girls. [16]
Butylbenzyl phthalate (BBzP)	Mono-benzyl phthalate (MBzP) Mono-butyl phthalate (MBP)	• Plasticizer in vinyl flooring, adhesives, food packaging, furniture upholstery, vinyl and carpet tiles, and artificial leather.	• Prenatal exposure associated with increased internalizing behaviors in 3 year olds. [15] • Concurrent exposure associated with increased risk of allergic diseases including rhinitis, asthma, and eczema. [11,17–19]
Di-(2-ethylhexyl) phthalate (DEHP)	Mono-ethyl-hexyl phthalate (MEHP) Mono-2-ethyl-5-oxo-hexyl phthalate (MEOHP) Mono-2-ethyl-5-hydroxyl-hexyl phthalate (MEHHP) Mono-2-ethyl-5-carboxy-pentyl phthalate (MECPP)	• Plasticizer for polyvinyl chloride plastics including medical tubing, some food packaging, plastic toys, shower curtains, rainwear, automobile upholstery, packaging film and sheets, and shoes.	• Prenatal exposure associated with decreased mental and physical development in 6 month olds. [14] • Prenatal exposure associated with decreased anogenital distance in male infants [12,20] and reductions in masculine play behavior among boys. [13] • Concurrent exposure associated with increased risk of allergic diseases including rhinitis, asthma, and eczema. [17,18]
Di-n-octyl phthalate (DnOP)	Mono-3-carboxy-propyl phthalate (MCPP)	• Plasticizer in polyvinyl chloride plastics. • Paints, lacquers, and adhesives.	• Studies report null associations with childhood health outcomes.

Phthalate (Abbreviation)	Metabolites Measured in Epidemiological Studies (Abbreviation) †	Uses in Commerce	Reported Health Effects in Infants/Children†
		• Flooring tiles.	
Di-isononyl phthalate (DiNP)	Mono-carboxy-iso-octyl phthalate (MCOP)	• Plasticizer in polyvinyl chloride plastics. • Paints, lacquers, and adhesives.	• Concurrent exposure associated with delayed pubarche in girls. [16] • Only one study of childhood health effects.
Di-isodecyl phthalate (DiDP)	Mono-carboxy-iso-nonyl phthalate (MCNP)	• Plasticizer in polyvinyl chloride plastics. • Paints, lacquers, and adhesives.	• No studies of health effects in children to date.

*See Sathyanarayana for a complete review of potential phthalate exposure sources [21].

†Note: not all metabolites for the parent diester are listed, only those used as a biomarker in epidemiologic studies