Environment International 115 (2018) 79–88

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Associations of prenatal environmental phenol and phthalate biomarkers with respiratory and allergic diseases among children aged 6 and 7 years

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ARTICLE INFO

Keywords:
Environmental phenols
Bisphenol A
Phthalates
Endocrine disruption
Asthma
Children's health

ABSTRACT

Background: Prenatal environmental phenol and phthalate exposures may alter immune or inflammatory responses leading to respiratory and allergic disease.
Objectives: We estimated associations of prenatal environmental phenol and phthalate biomarkers with respiratory and allergic outcomes among children in the Mount Sinai Children's Environmental Health Study.
Methods: We quantified urinary biomarkers of benzophenone-3, bisphenol A, paradichlorobenzene (as 2,5-dichlorophenol), triclosan, and 10 phthalate metabolites in third trimester maternal samples and assessed asthma, wheeze, and atopic skin conditions via parent questionnaires at ages 6 and 7 years (n = 164 children with 240 observations). We used logistic regression to estimate covariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) per standard deviation difference in natural log biomarker concentrations and examined effect measure modification by child's sex.
Results: Associations of prenatal 2,5-dichlorophenol (all outcomes) and bisphenol A (asthma outcomes) were modified by child's sex, with increased odds of outcomes among boys but not girls. Among boys, ORs for asthma diagnosis per standard deviation difference in biomarker concentration were 3.00 (95% CI: 1.36, 6.59) for 2,5-dichlorophenol and 3.04 (95% CI: 1.38, 6.68) for bisphenol A. Wheeze in the past 12 months was inversely associated with low molecular weight phthalate metabolites among girls only (OR: 0.27, 95% CI: 0.13, 0.59) and with benzophenone-3 among all children (OR: 0.65, 95% CI: 0.44, 0.96).
Conclusions: Prenatal bisphenol A and paradichlorobenzene exposures were associated with pediatric respiratory outcomes among boys. Future studies may shed light on biological mechanisms and potential sexually-dimorphic effects of select phenols and phthalates on respiratory disease development.

1. Introduction

Asthma is the leading chronic pediatric disease worldwide, causing substantial morbidity (Akinbami et al., 2016; Asher and Pearce, 2014). Emerging evidence suggests that exposures to environmental contaminants during the prenatal period may increase the risk of developing respiratory and allergic disease in childhood. Environmental exposures during early life can cause irreversible changes to the immune system and have been shown to alter lung development, reduce lung function, and increase respiratory illness and allergic manifestations later in life (Harding et al., 2009; Martino and Prescott, 2011; Miller and Marty, 2010). In particular, the role of estrogen in immune response suggests the potential for endocrine disrupting chemicals to influence development of asthma and allergic disease (Bonds and Midoro-Horiuti, 2013).

Some phenols, including bisphenol A, benzophenone-3, 2,5-dichlorophenol (a metabolite of paradichlorobenzene), and triclosan, as well as phthalates are synthetic environmental chemicals that may induce immunologic changes leading to adverse respiratory and allergic outcomes. Although these chemicals (or their precursors) are rapidly

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https://doi.org/10.1016/j.envint.2018.03.016
Received 15 December 2017; Received in revised form 10 March 2018; Accepted 11 March 2018

metabolized and excreted, their ubiquity in consumer products has led to widespread exposures in the general U.S. population (Centers for Disease Control and Prevention, 2017b). Bisphenol A is used in the manufacture of polycarbonate plastics and epoxy resins and can be detected in products such as canned foods and beverages, toys, and dental sealants. Benzophenone-3 is used as a UV filter in sun-blocking agents and plastics. Paradichlorobenzene, also known as 1,4-dichlorobenzene, is a disinfectant used in mothballs and deodorizers. Triclosan is an antibacterial agent found in products such as detergents, textiles, and personal care products. Low molecular weight phthalates (LMWPs) are contained in cosmetics, personal care products, and medications while high molecular weight phthalates (HMWPs) are used in plastic tubing, food packaging and processing materials, vinyl flooring, and building materials.

Prenatal bisphenol A and phthalate exposures are hypothesized to increase the risk of asthma and allergy by altering immune or inflammatory responses (Robinson and Miller, 2015), potentially via endocrine disruption (Bonds and Midoro-Horiuti, 2013). While the exact mechanisms by which these chemicals could impact development of respiratory and allergic disease are not well understood, early life bisphenol A and phthalate exposures in experimental animals may result in pro-inflammatory immune responses, allergic sensitization, and bronchial inflammation that may depend on exposure timing and offspring sex (Bauer et al., 2012; Chen et al., 2015; Han et al., 2014; Jahreis et al., 2017; Midoro-Horiuti et al., 2010; Nakajima et al., 2012; O'Brien et al., 2014; Petzold et al., 2014; Shin et al., 2014; Wang et al., 2017; Yanagisawa et al., 2008). In humans, several studies have reported a deleterious impact of prenatal bisphenol A exposure on respiratory outcomes in early childhood (Gascon et al., 2015; Spanier et al., 2012; Spanier et al., 2014b; Vernet et al., 2017; Zhou et al., 2017) while another study did not (Donohue et al., 2013). Similarly, most prospective birth cohort studies evaluating prenatal phthalate exposures have reported associations with respiratory and allergic outcomes, particularly for HMWPs (Gascon et al., 2015; Herberth et al., 2017; Jahreis et al., 2017; Just et al., 2012; Ku et al., 2015; Smit et al., 2015; Whyatt et al., 2014) though there are exceptions (Vernet et al., 2017; Wang et al., 2014).

Limited research suggests that early life exposures to other environmental phenols, including benzophenone-3, paradichlorobenzene, and triclosan, may also affect respiratory health. Although mechanistic studies are sparse, these environmental phenols may affect development or severity of asthma and allergic diseases via alteration of immune function or disruption of the gut or airway microbiome (Jerschow et al., 2012; Savage et al., 2012). Several cross-sectional studies have reported associations of 2,5-dichlorophenol and triclosan concentrations with increased asthma, asthma morbidity, and allergic sensitization (Bertelsen et al., 2013; Clayton et al., 2011; Jerschow et al., 2012; Jerschow et al., 2014; Savage et al., 2014; Savage et al., 2012; Spanier et al., 2014a). In the only prospective study, prenatal 2,5-dichlorophenol concentrations were associated with increased rates of wheeze, whereas benzophenone-3 was associated with decreased rates, in a French cohort of boys (Vernet et al., 2017).

In the current study, we sought to examine whether prenatal urinary concentrations of bisphenol A, benzophenone-3, 2,5-dichlorophenol, triclosan, and 10 phthalate metabolites were associated with respiratory and allergic disease among school-aged children participating in a prospective pregnancy cohort study in New York City. As a secondary aim, we assessed effect measure modification by child's sex.

2. Materials and methods

2.1. Study population

The Mount Sinai Children's Environmental Health Study is a prospective pregnancy cohort that enrolled pregnant women in New York City from 1998 to 2002. Details of this cohort have been described previously (Engel et al., 2007). Briefly, 479 primiparous women were enrolled from the Mount Sinai prenatal clinic and two adjacent private practices. Seventy-five women were excluded because of medical complications, very premature births (< 32 weeks gestation or < 1500 g), delivery of an infant with birth defects, inability to obtain biological specimens before delivery, change of residence, or refusal to continue participation. Trained research assistants collected maternal baseline sociodemographic and household characteristics during an in person, two-hour structured interview conducted at third trimester prenatal care visits. Delivery characteristics and infant sex were ascertained from a computerized perinatal database at Mount Sinai Hospital.

The final cohort consists of 404 mother-infant pairs for whom birth data are available. Urine specimens were collected from 401 women and there was sufficient volume for quantification of environmental phenols in 367 specimens and phthalates in 382. Following previous analyses of this cohort, we excluded participants with a creatinine concentration < 10 μg/dL ($n = 1$) due to the potential for inaccurate biomarker measurements (Wolff et al., 2008). Outcome data were available for 164 children who attended at least one follow-up visit at 6 or 7 years of age. If the child attended both visits, we included these repeated measures in analyses of symptoms in the past 12 months. Thus, the final sample size for our current study on respiratory and allergic disease outcomes consisted of 159 children with 232 observations for the environmental phenols analyses and 164 children with 240 observations for the phthalates analyses.

2.2. Human subjects

We obtained written informed consent from women prior to participation. At child follow-up visits, we obtained informed consent from the parent as well as assent from children aged 7 years. We received approval for the study from the Mount Sinai School of Medicine Institutional Review Board and for the present analysis from the University of North Carolina at Chapel Hill Institutional Review Board. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

2.3. Measurement of environmental phenol and phthalate biomarkers

To assess exposure to environmental phenols and phthalates, we collected a spot urine sample from participating women during their third trimester of pregnancy (mean = 31.5 weeks gestation, SD = 5.1 weeks, range = 25–40 weeks gestation). Samples were stored at –80 °C until shipment on dry ice to the CDC for quantification of creatinine, environmental phenols and phthalates biomarkers concentrations. Environmental phenol biomarkers included bisphenol A, benzophenone-3, 2,5-dichlorophenol, and triclosan. Phthalate biomarkers included monoisobutyl phthalate (MiBP, a metabolite of diisobutyl phthalate), mono-n-butyl phthalate (MnBP, a metabolite of di-n-butyl phthalate), monoethyl phthalate (MEP, a metabolite of diethyl phthalate), monobenzyl phthalate (MBzP, a metabolite of butyl benzyl phthalate), mono(3-carboxypropyl) phthalate (MCPP, a nonspecific metabolite of di-n-octyl phthalate and other HMWPs and a minor metabolite of dibutyl phthalate), and four metabolites of di(2-ethylhexyl) phthalate (DEHP): mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethylhexyl) phthalate (MEHP). Urine samples were analyzed for target analytes at the CDC using solid phase extraction coupled with high performance liquid chromatography–isotope dilution tandem spectrometry as described previously (Kato et al., 2005; Ye et al., 2005).