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Associations between prenatal maternal urinary concentrations of personal care product chemical biomarkers and childhood respiratory and allergic outcomes in the CHAMACOS study

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ABSTRACT

Background: Personal care product chemicals may be contributing to risk for asthma and other atopic illnesses. The existing literature is conflicting, and many studies do not control for multiple chemical exposures.
Methods: We quantified concentrations of three phthalate metabolites, three parabens, and four other phenols in urine collected twice during pregnancy from 392 women. We measured T helper 1 (Th1) and T helper 2 (Th2) cells in their children's blood at ages two, five, and seven, and assessed probable asthma, aeroallergies, eczema, and lung function at age seven. We conducted linear and logistic regressions, controlling for additional biomarkers measured in this population as selected by Bayesian Model Averaging.
Results: The majority of comparisons showed null associations. Mono-*n*-butyl phthalate (MnBP) was associated with higher Th2% (RR: 10.40, 95% CI: 3.37, 17.92), and methyl paraben was associated with lower Th1% (RR: −3.35, 95% CI: −6.58, −0.02) and Th2% at borderline significance (RR: −4.45, 95% CI: −8.77, 0.08). Monoethyl phthalate was associated with lower forced expiratory flow from 25 to 75% of forced vital capacity ($FEF_{25–75\%}$) (RR: −3.22 L/s, 95% CI: −6.02, −0.34). Propyl paraben (OR: 0.86, 95% CI: 0.74, 0.99) was associated with decreased odds of probable asthma.
Conclusions: While some biomarkers, particularly those from low molecular weight phthalates, were associated with an atopic cytokine profile and poorer lung function, no biomarkers were associated with a corresponding increase in atopic disease.

1. Introduction

Chemicals in personal care products, including some phthalates, parabens, and other phenols, may impact children's immune development and risk for asthma. Low molecular weight phthalates (diethyl phthalate (DEP), dibutyl phthalate (DBP), and diisobutyl phthalate (DiBP)) are used in fragrances, cosmetics, and medications (Kelley et al., 2011; Koniecki et al., 2011). Parabens (*e.g.*, methyl paraben, propyl paraben, butyl paraben) are used as preservatives in cosmetics, pharmaceuticals, and paper products because of their bactericidal and fungicidal properties (Guo and Kannan, 2013; Liao and Kannan, 2014). Triclosan, an antibacterial found in some toothpastes, deodorants, and antimicrobial fabrics (Dann and Hontela, 2011), was recently banned from antibacterial soaps for not being generally recognized as safe and effective (United States Food and Drug Administration, 2013). 2,4-Dichlorophenol is an intermediate in pesticide manufacturing, but is also a photo-degradation product of triclosan (Latch et al., 2005). 2,5-Dichlorophenol is used in moth balls and room and toilet deodorizers (Wei et al., 2014). Benzophenone-3, also known as oxybenzone, absorbs ultraviolet rays A and B and is used in sunscreens and other products for skin protection, and in cosmetics to prolong product durability (Han et al., 2016). Exposure to these chemicals or their precursors is widespread: low molecular weight phthalate metabolites were detected in the urine of 97% or greater of 2013–2014 National Health and Nutrition Examination Survey (NHANES) participants, and most phenols were detected in 96% or greater of participants (CDC, 2018).

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Rates of childhood asthma, aeroallergy, and eczema are high in the U.S. and have been increasing for several decades (Akinbami et al., 2009; Asher et al., 2006; Jackson et al., 2013). In the 2013–2014 NHANES, 15.9% of children had been diagnosed with asthma (CDC, 2013–2014), and in the 2005–2006 NHANES (the latest year for which this information is available) self-reported doctor diagnosis of aeroallergy and eczema prevalence were 24.6% and 14.3%, respectively (CDC, 2005–2006). Activity of T helper cells lymphocytes may be involved in the biological mechanisms of asthma, inhalant allergies, and other allergic diseases (Barnes, 2001; Deo et al., 2010). T helper cells release cytokines that send chemical messages to other immune cells (Zhu and Paul, 2008). Of the two main types of T helper cells, T helper 1 (Th1) cells combat intracellular viruses and bacteria through cell-mediated immunity and secrete cytokines such as interferon gamma (IFN-y), interleukin-2 (IL-2), and IL-3, while T helper 2 (Th2) cells are involved in allergic and inflammatory responses and secrete cytokines such as IL-4, IL-5, and IL-6 (Volcheck, 2008). A higher ratio of Th2 cytokines to Th1 cytokines has been associated with increased risks of aeroallergy and asthma (Barnes, 2001; Deo et al., 2010), suggesting a possible mechanism of asthma and allergy development.

Some animal and *in vitro* studies suggest exposure to low molecular weight phthalates leads to higher Th2 cytokine concentrations (Li et al., 2014; Maruyama et al., 2007; Shigeno et al., 2009). DEP and DBP also propagate the release of inflammatory cytokines *in vitro* directly from airway epithelial cells which then lead to proliferation and migration of bronchial smooth muscle cells (Kuo et al., 2011). These are key steps in the airway remodeling that characterizes asthma (Glue et al., 2005) and they may occur prenatally (Bousquet et al., 2004; Kumar, 2008). Parabens, triclosan, and benzophenone-3 exposure also leads to higher Th2 cytokine concentrations *in vitro* or in animals (Anderson et al., 2012; Hegazy et al., 2015; Jannesson et al., 2004; Kato et al., 2006; Kwon et al., 2013; Marshall et al., 2015), and animal studies suggest that exposure to triclosan leads to reduced lung function (Anderson et al., 2012). Phthalates and parabens are xenoestogens (Harris et al., 1997; Routledge et al., 1998), which have been shown to lower forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) and increase airway hyperresponsiveness (Bonds and Midoro-Horiuti, 2013), as well as encourage Th2 differentiation and other allergic inflammatory responses (Bonds and Midoro-Horiuti, 2013). Exposures to low molecular weight phthalates, parabens, and phenols (or their precursors) are also associated with increased biomarkers of oxidative stress in humans (Ferguson et al., 2014; Ferguson et al., 2011; Holland et al., 2016; Watkins et al., 2015) and *in vitro* (Bukowska, 2003; Gao et al., 2013; Lourenço et al., 2015; Xu et al., 2013) which can play a crucial role in asthma development (Kato et al., 2006) by increasing inflammation and promoting airway hyperresponsiveness (Cho and Moon, 2010). Maternal oxidative stress *in utero* can lead to epigenetic effects in pregnancy, the induction of fetal proinflammatory genes (Martino and Prescott, 2011), and increased fetal oxidative stress that can affect the development of the fetal immune and respiratory systems (Leon Hsu et al., 2015).

Some epidemiologic studies on prenatal exposure to these chemicals have found an association with atopic outcomes. A study of 154 children found that prenatal maternal urinary concentrations of mono-*n*-butyl phthalate (MnBP) were associated with increased risk of asthma from ages 5–11 (Whyatt et al., 2014), and in 610 children, prenatal maternal urinary concentrations of mono-isobutyl phthalate (MiBP) were associated with dermatitis at age 3 (Herberth et al., 2017). However, prenatal urinary concentrations of low molecular weight phthalates were not associated with asthma, or eczema in 164 children ages 6 and 7 (Buckley et al., 2018). Prenatal parabens were associated with asthma and wheeze in Vernet et al.'s study of 587 five-year-olds (Vernet et al., 2017), but not with asthma, wheeze, or aeroallergy in Lee-Sarwar et al.'s study of 467 three- and four-year-olds (Lee-Sarwar et al., 2017). In Vernet et al.'s study (Vernet et al., 2017), 2,5-dichlorophenol was associated with wheeze, and it was associated with eczema in Lee-Sarwar et al.'s study (Lee-Sarwar et al., 2017).

Phthalates, parabens, and some other phenols have been detected in human placentas, furthering the case for studying these exposures prenatally (Mose et al., 2007; Valle-Sistac et al., 2016). Pregnancy also represents a susceptible window of exposure, as much of the immune and respiratory systems develop *in utero*. To further elucidate the relationships between exposures to these chemicals and childhood asthma and atopy, we measured urinary concentrations of three phthalate metabolites, three parabens, and four other phenols in maternal urine collected at two time points during pregnancy and analyzed associations with asthma, aeroallergies, eczema, and lung function in their children at age seven, and with T helper cells at ages two, five, and seven. We analyzed data from a unique study population and employed Bayesian Model Averaging to control for confounding by co-exposure to pollutants, addressing gaps in previous literature.

2. Methods

2.1. CHAMACOS study

Participants were enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal cohort study examining the effects of *in utero* and childhood environmental exposures on growth, neurodevelopment, respiratory disease, and pubertal development in the Salinas Valley, California, an agricultural community. English or Spanish-speaking mothers who were eligible for low-income health insurance (MediCal), at least 18 years old, < 20 weeks' pregnant, and who were planning on delivering at the county hospital were recruited to participate in the study in 1999–2000 from prenatal care clinics serving the Latino, farmworker population in the Salinas Valley. A total of 601 mothers were enrolled and 531 were followed through the birth of a live infant. Of those, 517 had at least one prenatal measurement of low molecular weight phthalates, parabens, or other phenols and 392 children additionally had information on respiratory or allergy symptoms, spirometry, or cytokine measurements. These 392 children did not differ substantially in demographics or in maternal urinary biomarker concentrations compared to children who were lost to follow-up and did not have outcome data. Research protocols were approved by the Office for the Protection of Human Subjects (OPHS) at UC Berkeley. The Centers for Disease Control and Prevention (CDC) deferred to OPHS. Mothers provided written informed consent and children provided verbal assent at age seven.

2.2. Exposure assessment

Spot urine samples were collected from mothers at the time of the two pregnancy interviews in 1999–2000. Samples were collected in phthalate-free polypropylene urine cups, aliquoted into glass vials, and stored at −80 °C until shipment to the CDC in Atlanta, Georgia for analysis. Urinary specific gravity was measured using a hand-held refractometer (National Instrument Company Inc., Baltimore, MD). We corrected for urinary dilution using the formula: (analyte concentration ∗ (1.024 − 1)/(sample specific gravity − 1)) (Cone et al., 2009).

Missing specific gravity values were imputed for 81 participants by regressing specific gravity on creatinine and multiplying the coefficient by existing creatinine values to generate missing specific gravity values, and sensitivity analyses were run excluding the women with imputed specific gravity.

Solid phase extraction coupled with isotope dilution high performance liquid chromatography- tandem mass spectrometry was used to quantify concentrations of the following three phthalate metabolites and eight phenols: monoethyl phthalate [MEP, a metabolite of DEP]; MnBP, a metabolite of DBP; and MiBP, a metabolite of DiBP; methyl paraben; propyl paraben; butyl paraben; triclosan; benzophenone-3; 2,4-dichlorophenol; and 2,5-dichlorophenol. Butyl paraben was dropped from analyses because it was only detected in 67% of