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Predictors of urinary flame retardant concentration among pregnant women

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ABSTRACT

Background: Organophosphate compounds are commonly used in residential furniture, electronics, and baby products as flame retardants and are also used in other consumer products as plasticizers. Although the levels of exposure biomarkers are generally higher among children and decrease with age, relatively little is known about the individual characteristics associated with higher levels of exposure. Here, we investigate urinary metabolites of several organophosphate flame retardants (PFRs) in a cohort of pregnant women to evaluate patterns of exposure.
Methods: Pregnant North Carolina women (n = 349) provided information on their individual characteristics (e.g. age and body mass index (BMI)) as a part of the Pregnancy Infection and Nutrition Study (2002–2005). Women also provided second trimester urine samples in which six PFR metabolites were measured using mass spectrometry methods.
Results: PFR metabolites were detected in every urine sample, with BDCIPP, DHPH, ip-PPP and BCIPHIPP detected in >80% of samples. Geometric mean concentrations were higher than what has been reported previously for similarly-timed cohorts. Women with higher pre-pregnancy BMI tended to have higher levels of urinary metabolites. For example, those classified as obese at the start of pregnancy had ip-PPP levels that were 1.52 times as high as normal weight range women (95% confidence interval: 1.23, 1.89). Women without previous children also tended to have higher urinary levels of DPHP, but lower levels of ip-PPP. In addition, we saw strong evidence of seasonal trends in metabolite concentrations (e.g. higher DPHP, BDCIPP, and BCIPHIPP in summer, and evidence of increasing ip-PPP between 2002 and 2005).
Conclusions: Our results indicate ubiquitous exposure to PFRs among NC women in the early 2000s. Additionally, our work suggests that individual characteristics are related to exposure and that temporal variation, both seasonal and annual, may exist.

1. Introduction

Flame retardant chemicals have been added to a variety of household products to meet flammability standards for decades. Until the mid-2000s, polybrominated diphenyl ethers (PBDEs) accounted for a large proportion of flame retardants used in household products including polyurethane foam and electronics; however, regulatory action and concern over the persistence, bioaccumulation, and toxicity of PBDEs led to an increased use of alternative flame retardants (Stapleton et al., 2012b; Van der Veen and de Boer, 2012). Organophosphate flame retardants (PFRs) are now among the most commonly used PBDE alternatives in industries that manufacture residential furniture, electronics (e.g. TVs) and baby products (e.g. nursing pillows). They are commonly added to flame retardant mixtures, such as Firemaster® 550 (FM550), and to other consumer products as plasticizers (Ballesteros-Gomez et al., 2014; Fang et al., 2013; Patisaul et al., 2013; Stapleton et al., 2008; Stapleton et al., 2009; Stapleton et al., 2011).

PFRs have been detected with high frequency in recent studies of home, office, and automobile dust, demonstrating that they leach from products and suggesting ubiquitous exposure [e.g. (Brandsma et al., 2013; Brommer and Harrad, 2015; Cao et al., 2014; Carignan et al., 2013; Cristale et al., 2016; Hoffman et al., 2015b; Stapleton et al., 2008; Stapleton et al., 2009; Stapleton et al., 2011)]. Additionally, an accumulating body of research indicates that the vast majority of U.S. adults (>90%) have detectable levels of PFR metabolites in their urine, and similar detection frequencies have been reported in Canadian,

Abbreviations: (BCIPHIPP), 1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate; (BMI), body mass index; (BCIPP), bis(1-chloro-2-propyl) phosphate; (BDCIPP), bis(1,3-dichloro-2-propyl) phosphate; (CI), confidence interval; (DPHP), diphenyl phosphate; (FM550), Firemaster® 550; (GM), geometric mean; (ip-PPP), isopropyl-phenyl phenyl phosphate; (MDL), method limit of detection; (PFRs), organophosphate flame retardants; (PBDEs), polybrominated diphenyl ethers; (PIN), Pregnancy Infection and Nutrition Study; (tb-PPP), tert-butyl phenyl phenyl phosphate.

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European, Asian and Australian populations (e.g. (Butt et al., 2014 and Butt et al., 2016; Cequier et al., 2015; Dodson et al., 2014; Hoffman et al., 2014; Hoffman et al., 2015a; Hoffman et al., 2015b; Kosarac et al., 2016; Meeker et al., 2013; Van den Eede et al., 2015; Su et al., 2015)). Although data suggest that metabolite levels vary by age, with younger individuals shown to have higher exposures (e.g. Butt et al., 2014 and Butt et al., 2016; Hoffman et al., 2015a; Van den Eede et al., 2015), the individual characteristic and behaviors associated with higher levels of exposure are not well understood.

In our present work we investigate the levels of exposure in a large pregnancy cohort, and additionally assess factors associated with higher levels of PFR metabolites in urine samples. We focus on widely used PFRs and six metabolites (Fig. 1). Identifying factors contributing to higher levels of exposure to these compounds is particularly important because certain PFRs can disrupt normal endocrine function (Liu et al., 2012; Wang et al., 2013; Meeker et al., 2013 and Meeker and Stapleton, 2010), are carcinogenic (Faust and August, 2011; Gold et al., 1978), neurotoxic (Dishaw et al., 2011), reproductive toxicants (Meeker et al., 2013 and Meeker and Stapleton, 2010; Liu et al., 2013; Farhat et al., 2013), and potentially adipogenic (Patisaul et al., 2013; Pillai et al., 2014). In addition, recent data suggests that PFRs may have similar or greater toxicity than their PBDE predecessors, particularly with respect to neurodevelopmental outcomes (Behl et al., 2015; Behl et al., 2016).

2. Methods

2.1. Study population

The Pregnancy Infection and Nutrition (PIN) Study enrolled a cohort of central North Carolina women in early pregnancy and conducted follow-up through delivery (PIN, 2012). PIN women were recruited from the University of North Carolina prenatal care clinic, and delivered their infants at University of North Carolina hospitals between 2001 and 2006 (n = 2009; PIN phase 3). This analysis is part of a larger project investigating the impacts of exposure to environmental chemicals on children's growth. This sample is limited to 349 mothers recruited during the final four years of the cohort study, whose children had growth measurements collected at multiple time points (infants born 2002–2005). Self-administered questionnaires, telephone interviews, and home visits were used to collect pregnancy and postpartum health and lifestyle information throughout pregnancy and after the child's birth (PIN, 2012). All study protocols were approved by the institutional review board at the University of North Carolina at Chapel Hill and all mothers provided informed consent prior to completing any study activities.

2.2. Urine collection and analysis

During the late-second or early-third trimester, PIN women collected a spot urine sample in a standard urine collection cup. The time and date of collection was recorded, and urine samples were aliquoted into polyethylene storage tubes and frozen at −80 °C until analysis.

Urine samples were extracted using enzyme deconjugation and solid phase extraction (SPE) techniques as previously described (Van den Eede et al., 2013) but adapted for 5 ml of urine (Butt et al., 2016). In brief, samples were thawed, 5 ml of urine were aliquoted into a clean glass test tube, the internal standard mixture was spiked (10 ng of d_{10}-BDCIPP, 8.8 ng of d_{10}-DPHP; 25 ng of d_{12}-TCEP) and samples vortexed. After pH adjustment with sodium acetate (1.75 ml of 1 M sodium acetate, pH 5), the enzyme solution was added (250 μl of1000 units/ml β-glucuronidase, 33 units/ml sulfatase in 0.2 M sodium acetate buffer), and the samples were vortexed and incubated overnight in a 37 °C water bath. Samples were extracted and cleaned using SPE with a StrataX-AW (60 mg, 3 ml) column, and were reconstituted in 500 μl of 1:1 water:methanol, as previously described (Butt et al., 2016). Internal standard recovery was quantified by spiking with $^{13}C_2$-DPHP.

Extracts were analyzed using electrospray ionization (ESI) liquid chromatography tandem mass spectrometry (LC-MS/MS) with a Phenomenex Luna C18 column on an Agilent 1100 series LC and an Agilent 6410B tandem mass spectrometer as previously described (Butt et al., 2014 and Butt et al., 2016). Data were acquired under multiple reaction monitoring conditions using optimized parameters. Analyte responses were normalized to internal standard responses. BCIPP and BDCIPP were normalized using d_{10}-BDCIPP, DPHP, ip-PPP and tb-

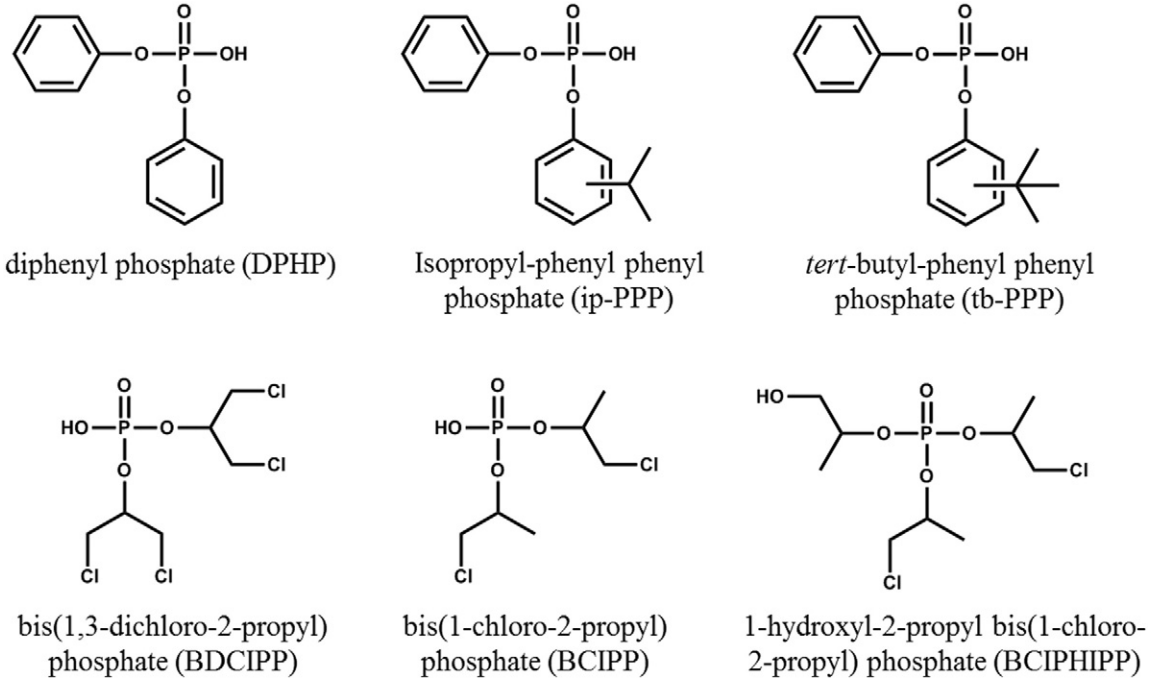

Fig. 1. Chemical structures of urinary PFR metabolites monitored. TPHP metabolite = DPHP; Isopropyl-phenyl diphenyl phosphate metabolite = ip-PPP; Tertbutyl-phenyl diphenyl phosphate metabolite = tb-PPP; TDCIPP metabolite = BDCIPP; and tris(1-chloro-2-isopropyl) phosphate (TCIPP metabolites) = BCIPP and BCIPHIPP.