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Associations between urinary diphenyl phosphate and thyroid function

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ABSTRACT

Triphenyl phosphate (TPHP) is a commonly used organophosphate flame retardant and plasticizer with widespread human exposure. Data on health effects of TPHP are limited. Recent toxicological studies suggest TPHP may alter thyroid function. We used repeated measures to assess the temporal variability in urinary concentrations of the TPHP metabolite, diphenyl phosphate (DPHP), and to examine relationships between DPHP concentrations and thyroid hormones. We sampled 51 adults at months 1, 6, and 12 from 2010 to 2011. Urine samples were analyzed for DPHP. Serum samples were analyzed for free and total thyroxine (fT_4, TT_4), total triiodothyronine (TT_3), and thyroid stimulating hormone (TSH). We assessed variability in DPHP using intraclass correlation coefficients (ICCs) and kappa statistics. We used linear mixed-effects models to examine associations between DPHP and thyroid hormones. DPHP was detected in 95% of urine samples. Mean DPHP concentrations were 43% higher in women than men. DPHP showed high within-subject variability (ICC range, 0.13–0.39; kappa range, 0.16–0.39). High versus low (≥2.65 vs. <2.65 ng/mL) DPHP in all participants was associated with a 0.43 μg/dL (95% confidence interval: 0.15, 0.72) increase in mean TT_4 levels. In sex-stratified analyses, high versus low DPHP was associated with a 0.91 μg/dL (95% CI: 0.47, 1.36) increase in mean TT_4 in women. The association was attenuated in men (βeta = 0.19; 95% CI: −0.15, 0.52). We found no significant associations between DPHP and fT_4, TT_3, or TSH. We found evidence that TPHP exposure may be associated with increased TT_4 levels, especially in women.

1. Introduction

Organophosphate flame retardants are widely used in commercial and consumer products (van der Veen and de Boer, 2012). Their use has increased over the past decade, in part due to the phase out of certain polybrominated diphenyl ethers (PBDEs) such as PentaBDE (EPA, 2008). Triphenyl phosphate (TPHP, CAS no. 115-86-6) is an organophosphate ester used both as a flame retardant and plasticizer, and has been applied to polyurethane foam, resins, polyvinylchloride (PVC), hydraulic fluids, lacquers, and nail polish (Mendelsohn et al., 2016; van der Veen and de Boer, 2012). Like PBDEs, TPHP is used as a chemical additive, implying that it is not chemically bound to the source material and can escape from products and enter the surrounding environment. TPHP has been detected frequently in the indoor environment (Dodson et al., 2014; Hoffman et al., 2015b; Meeker et al., 2013b). Humans may be exposed to TPHP through inhalation, ingestion of indoor dust, and dermal absorption through contact with dust, source materials, or direct partitioning from vapor (Pillai et al., 2014). The half-life of TPHP in humans is unknown, but is thought to be on the order of hours to days (Hou et al., 2016). However, because of its widespread use and ubiquity in the indoor environment, exposures may be relatively constant over time. Constant exposure could theoretically create "pseudo-persistence" in the human body, meaning levels of urinary metabolites of TPHP would be fairly stable, despite TPHP's short half-life.

Methods have been developed to measure diphenyl phosphate (DPHP), a urinary metabolite of TPHP. As a biomarker of TPHP exposure, urinary DPHP concentrations have been characterized in a growing number of studies, with most U.S. studies reporting ubiquitous detection of DPHP (Butt et al., 2014, 2016; Dodson et al., 2014; Hoffman et al., 2014, 2015b; Meeker et al., 2013b). While the majority of U.S. studies have been conducted in adults, three recent studies measured levels of urinary DPHP in children (Butt et al., 2014, 2016; Hoffman et al., 2015a). Four studies have assessed intra-individual variability of urinary DPHP via repeated measures (Cequier et al., 2015; Hoffman et al., 2014, 2015b; Meeker et al., 2013b). However, most of these studies had small sample sizes with short sampling periods that may not capture potential long term or seasonal variability.

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Despite growing evidence of widespread human exposure, relatively little is known about the potential human health effects of TPHP. Preliminary toxicology studies suggest that TPHP may disrupt thyroid function (Kim et al., 2015; Kojima et al., 2013; Liu C et al. 2013; Liu et al., 2016). Healthy thyroid function is critical for fetal and child growth and development and for maintaining important bodily systems in adults such as metabolism, mental health and cognition, and reproduction (Taylor et al., 2013). There is increasing evidence that even subclinical changes in adult thyroid function may be associated with adverse effects (Taylor et al., 2013). To date only two studies have examined associations between TPHP exposure and thyroid function in humans (Meeker and Stapleton, 2010; Meeker et al., 2013a). These cross-sectional analyses were both conducted in a small cohort of men from subfertile couples residing in the Boston, Massachusetts (MA) USA area. Additional studies are needed to further explore the potential relationship between TPHP exposure and thyroid function in larger and mixed sex study populations.

TPHP may share exposure sources and routes with PBDEs (Stapleton et al., 2012) and were positively correlated in household dust samples in a recent North Carolina study (Hoffman et al., 2015b). There is a growing literature linking PBDE exposure to thyroid disruption (Czerska et al., 2013; Linares et al., 2015), including previous work in the current study cohort (Makey et al., 2015). Therefore, it is important to consider potential confounding and/or modification by PBDEs when assessing associations between TPHP exposure and thyroid function.

The current study aims to characterize urinary DPHP concentrations in a population of U.S. adults, assess intra-individual variability of repeated DPHP measures, and investigate the association between adult DPHP concentrations and thyroid function. We measured urinary DPHP and serum thyroid hormones in repeated samples from a group of 51 male and female office workers over a one-year period as part of a study investigating exposure patterns and health effects of flame retardant chemicals in the Boston, MA area. We hypothesized that there would be high intra-individual variability in urinary DPHP concentrations over the study period and that DPHP concentrations would be associated with altered serum thyroid hormone levels. We explored whether factors including PBDEs, urinary iodine, age, or sex might modify associations between DPHP and thyroid hormones. Additionally, we characterized urinary DPHP concentrations at a single time point in a subset of the study participants' children.

2. Methods

2.1. Study participants

Study subjects were part of the Flame Retardant Exposure Study (FlaRE), which has been described previously (Makey et al., 2014). Briefly, a convenience sample of 26 male and 26 female office workers and a subset of their children (n = 14), were recruited from the Boston, MA metropolitan area. The fourteen children included some siblings, corresponding to nine FlaRE adults. Eligible adult participants were over the age of 18, nonsmokers, self-described as healthy, and planning to remain in the Boston area for the duration of the study period. Participants were excluded if they had a current or prior diagnosis of thyroid disease, male reproductive disease, or were pregnant. Serum and urine samples were collected from adults during three sampling rounds every six months from January 2010 to May 2011, representing Winter 2010, Summer 2010, and Winter 2011. Questionnaires were administered at each sample round to collect demographic, health, and lifestyle information. During the final sampling round, children provided urine samples, and questionnaires were administered to parents to collect children's demographic and behavioral information. Of the 52 adult participants, 41 completed all three sampling rounds, nine completed two rounds, and two completed one round. Samples were excluded from analysis for the following reasons: pregnancy (1 sample from 1 person), thyroid altering medication use (3 samples from 1 person), and no corresponding blood sample (4 samples from 4 people). PBDE data were excluded for one sample due to suspected field contamination during collection. The levels of hexaBDEs in the sample were ten times those in the individual's other two samples, while levels of the lower brominated congeners were similar across all three samples, suggesting contamination with residential dust containing the octaBDE commercial mixture. The final study population consisted of 51 adult participants (135 paired urine and serum samples) and 14 children (14 urine samples).

The Boston University Medical Center Institutional Review Board approved the study protocol. All participants provided informed consent and children provided informed assent to participate.

2.2. Urine samples

A single 90 mL spot urine sample was collected from each participant during each of the three sampling rounds. Samples were measured for specific gravity (SG) using a refractometer and aliquoted before being stored at −20 °C prior to analysis. Urinary DPHP was measured at Duke University using previously published methods (Cooper et al., 2011). Briefly, DPHP was extracted from urine using a mixed-mode anion exchange solid-phase extraction cartridge and then analyzed using atmospheric pressure chemical ionization liquid chromatography-tandem mass spectrometry (Cooper et al., 2011). Deuterated diphenyl phosphate (d10-DPHP) was used as the internal standard for quantification. The limit of detection (LOD) was calculated as three times the standard deviation of the laboratory blanks and ranged from 0.13–0.21 ng/mL across rounds. Sample DPHP values were blank corrected and values below the LOD (adults: n = 7, 5%; children: n = 0, 0%) were replaced with the LOD/$\sqrt{2}$. All samples were also analyzed for urinary iodine concentrations at the Boston University School of Medicine, Section of Endocrinology, Diabetes, and Nutrition using previously published methods (Valentin-Blasini et al., 2005). The coefficient of variation (CV) for iodine measurements was <5%. To account for urinary dilution, we SG corrected DPHP and iodine concentrations in all analyses except for modeling predictors of DPHP, where we included SG as an independent predictor (Boeniger et al., 1993). One sample with an extremely low SG (1.0001) was excluded from SG-corrected analyses due to the uncertainty surrounding the resulting extreme SG-corrected value.

2.3. Blood samples

A single 30 mL non-fasting blood sample was drawn from each study participant during each of the three sampling rounds. Serum samples were stored in amber glass vials at −80 °C prior to analysis. Samples from all rounds were analyzed at the Centers for Disease Control and Prevention (CDC) for PBDEs using previously published methods (Sjödin et al., 2004), and for total serum lipids as previously described (Makey et al., 2014). PBDE concentrations were standardized to total serum lipid concentrations (ng PBDE/g lipid). Samples from all rounds were analyzed for thyroid function at the Boston University School of Medicine, Section of Endocrinology, Diabetes, and Nutrition. Thyroid peroxidase antibody (TPOAb) was measured using immunometric enzyme immunoassay (Orgentec Diagnostika). Thyroid stimulating hormone (TSH), free thyroxine (fT_4), total thyroxine (TT_4), and total triiodothyronine (TT_3) were measured using enzyme-linked immunosorbent assays (Immuno-Biological Laboratories, Inc). Assay reference ranges were: TT_4 (women: 4.8–11.6 μg/dL, men: 4.4–10.8 μg/dL), fT_4 (0.8–2.0 ng/dL), TT_3 (0.52–1.85 ng/mL), TSH (0.4–4.2 mIU/L). TPOAb was categorized as normal (≤50 IU/mL) or elevated (>50 IU/mL).

2.4. Statistical analysis

Concentration distributions of DPHP, TSH, TT_3, and fT_4 were skewed and natural log (ln)-transformed when used as dependent variables.