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Exposure to polybrominated diphenyl ethers and phthalates in healthy men living in the greater Montreal area: A study of hormonal balance and semen quality

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ABSTRACT

Studies investigating the associations between exposure of young men to polybrominated diphenyl ethers (PBDEs) or phthalates and hormone levels or semen quality have produced inconsistent results. Our goal was to investigate the association of exposure to PBDEs or phthalate metabolites with changes in markers of thyroid (TSH, free T3 and free T4) and reproductive function (sperm concentrations, motility, and quality; serum LH and testosterone) in 153 healthy young men from the greater Montreal area. Using covariate-adjusted models, we found that each 10-fold increase in BDE-47 was associated with lower TSH levels (−17.3%; 95% CI: −31.5, 0.0; p = 0.05). BDE-47 exposure was also associated with a decrease in sperm concentration (−19.7%; 95% CI: −36.8; 2.0; p = 0.07) and motility (−25.5%; 95% CI: −44.5, 0.1; p = 0.05). Trends towards decreases in these parameters were also observed in association with exposure to BDE-100 and the sum of BDE-47, -99, and -100 (Σ_3BDEs). These associations were not accompanied by effects on sperm chromatin quality, as assessed with the HT-COMET assay. There were no substantial associations between urinary phthalate metabolite concentrations, either individually or grouped by molecular weight or parent compound, and sperm quality parameters; however, there was a positive association between elevated MECCP and free T4 (0.98; 95% CI: 0.02, 1.94; p = 0.05). Inverse associations between BDE-47 and Σ_3BDEs and free T3 and positive associations between MEHP and free T3 were stronger among individuals with BMI ≥ 25, suggesting that weight status may modify the effects of these endocrine disrupting chemicals.

1. Introduction

There is growing scientific, governmental and public concern that ubiquitous exposure to certain industrial compounds, grouped under the term endocrine disrupting chemicals (EDCs), may alter hormone homeostasis and affect human reproductive health. EDCs include polybrominated diphenyl ethers (PBDEs), organobromine compounds formerly used as flame retardants in building materials, electronics, furnishing, and textiles (Segev et al., 2009), and phthalic acid esters (phthalates), used as emollients, solvents, matrices and excipients in personal care products, construction materials, toys, packaging films and sheets, medical tubing and blood storage bags (Heudorf et al., 2007; Schettler, 2006). Because they are not covalently bound to their supports, both PBDEs and phthalates leach from their matrices into the environment, leading to widespread human exposure *via* ingestion, inhalation and dermal routes (Johnson-Restrepo and Kannan, 2009; Meeker et al., 2009c; Wittassek et al., 2011). Despite regulatory actions and voluntary withdrawals, lipophilic PBDE congeners persist in the

Abbreviations: PBDEs, polybrominated diphenyl ethers; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine; WHO, World Health Organization

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environment, biomagnify in the food chain, and bioaccumulate in breast milk, serum, and adipose tissue (Hites, 2004). Although phthalates are not persistent, biomonitoring studies reveal that their metabolites are detected widely, in urine, breast milk, cord blood and amniotic fluid (Latini et al., 2003; Main et al., 2006).

In animal studies, both the PBDEs and phthalates have been well established to disrupt hormones and adversely affect male reproductive parameters. In the rat, exposure to PBDEs during gestation or postnatally induces hypothyroidism and can produce a delay in puberty, reduced sperm count and reduced fertility (reviewed in Linares et al., 2015). In humans, these endpoints have been examined in several epidemiological studies conducted in populations with high exposure, such as anglers or e-waste recycling workers (Dallaire et al., 2009; Hagmar et al., 2001; Turyk et al., 2008; Zheng et al., 2017). However, the results of studies investigating associations between PBDE congeners and thyroid hormone levels have been inconsistent (Abdelouahab et al., 2011; Bloom et al., 2008; Dallaire et al., 2009; Hagmar et al., 2001; Makey et al., 2016; Turyk et al., 2008; Zheng et al., 2017). Small cohort studies in men recruited from fertility clinics also have reported inconsistent associations between exposure to PBDEs and reproductive hormone levels (Johnson et al., 2013; Meeker et al., 2009b) or sperm motility (Abdelouahab et al., 2011), while exposure to BDE-47 or BDE-153 among the partners of pregnant women from Greenland, Poland or Ukraine was not found to be associated with male semen quality or reproductive hormones (Toft et al., 2014). Thus, there is a need for further studies on healthy male populations.

The anti-androgenic effects of phthalates have been well described in animal models (reviewed in Albert and Jégou, 2014). Most observational studies in men show limited or weak evidence of a relationship between exposure to phthalates and impaired semen quality, but negative associations with androgen production in adulthood (Bloom et al., 2015; Duty et al., 2003, 2004; Hauser et al., 2006, 2007; Herr et al., 2009; Joensen et al., 2012; Jönsson et al., 2005; Jurewicz et al., 2013; Meeker et al., 2009a; Mendiola et al., 2011, 2012; G. Pan et al., 2006; Y. Pan et al., 2015; Pant et al., 2008; Specht et al., 2014; Thurston et al., 2016; Wirth et al., 2008). Importantly, the majority of these studies were conducted in men seeking infertility treatment. Since endocrine function in these men may differ from that in the general population, they may respond differently to endocrine disruption.

Hence, few studies have been done for either the PBDEs or phthalates in healthy men at the peak of their reproductive potential. We herein sought to investigate whether exposure to either PBDEs (based on hair concentrations) or phthalates (based on urinary metabolite concentrations) is associated with changes in markers of thyroid and reproductive function in young healthy men from the greater Montreal area. These markers include serum hormone levels and semen quality parameters, as defined by the World Health Organization (WHO) guidelines (World Health Organization, 2010), as well as sperm chromatin quality, as assessed by a novel automated approach (HT-COMET, Albert et al., 2016). Since PBDEs are lipophilic and bioaccumulate, we also evaluated whether any association between chemical exposures and markers of reproductive and thyroid function might be modified by the body mass index (BMI).

2. Materials and methods

2.1. Sample collection

From 2009 to 2012, 153 men aged between 18 and 41 years were recruited through advertisement (social media, public advertisement posters in university and community sites, local newspaper in the greater Montreal area) and provided informed consent. Participants completed a standardized health questionnaire including information on self-reported educational status (highest degree completed), age, weight and height, country of birth, ethnicity, marital status, smoking and drinking frequency, and total household income. We calculated body mass index (BMI) as weight/height^2. Individuals were classified as overweight if their BMI was equal to or > 25. Additionally, all participants provided a semen sample by masturbation after 3–5 days of abstinence. In addition to the absence of any co-morbidities that required long-term (> 6 month) medical therapies and monitoring, all participants had either (i) a recent history (< 1 year) of achieving an ongoing uncomplicated natural pregnancy with their female partner and semen parameters meeting the WHO reference values for normozoospermia (World Health Organization, 2010), or (ii) a sperm concentration over 45×10^6 cells/mL (3 times the WHO reference value) with no other parameter below the WHO reference values and no history of infertility. A 500 µL aliquot of semen was frozen and kept at −80 °C for subsequent use. A 50–100 mg hair sample, collected by cutting within 1 cm from the scalp at the posterior vertex using stainless steel scissors (Aleksa et al., 2012), was stored in sealed envelopes in the dark at 4 °C until assayed for PBDEs at The Hospital for Sick Children of Toronto. Early in the morning, serum and urine samples were obtained from each participant for immediate hormone analysis or storage at −20 °C for subsequent phthalate metabolite measurement, respectively. This study was conducted with ethics approval from the McGill University Hospital Centre Institutional Review Board (A01-M14-10B).

2.2. Sperm concentration and motility assessment

Computer-assisted semen analysis (CASA) was performed according to WHO guidelines using the SpermVision® software (12520/7000). Based on the clinical assumption that the motile portion of sperm is more indicative of the fertility potential in a semen sample than the total sperm population, we have reported the motile sperm index determined for each sample as the product of sperm concentration and percentage of total motility plus 1% (García et al., 2015). This parameter indicates the motile sperm portion in each semen sample for comparative and analytical purposes.

2.3. Hormone level measurements

Serum quantitative analyses were done for luteinizing hormone (LH), total testosterone, thyroid-stimulating hormone (TSH), free triiodothyronine (T3) and free thyroxine (T4) using immuno-enzymatic chemiluminescent assays (Beckman Coulter Inc., Brea, CA) as per the manufacturer's instructions. The amount of analyte in each sample was determined from a stored, multi-point calibration curve.

2.4. Chemical analysis of PBDE congener levels in hair

Hair was used as a matrix to assess PBDE exposure; previous studies have reported a positive correlation between serum and hair PBDE concentrations, especially for tetra- to hexa-BDE congeners (Poon et al., 2014; Zheng et al., 2014). To standardize the hair analyses, PBDEs were measured in the first 3–4 cm of hair closest to the root. The methodology for adult hair PBDE measurements was established previously (Aleksa et al., 2012; Carnevale et al., 2014; Goodyer et al., 2017; Poon et al., 2014). In brief, samples were analyzed by GC–MS for eight PBDE congeners: BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183 and BDE-209. The limits of detection (LOD) ranged from 1 to 4 ng/g and the limits of quantification (LOQ) from 3 to 12 ng/g. Analyses were limited to those congeners with quantification frequencies > 50% (BDE-47, -99, -100, and -209). BDE-28, -153, and -154 were expressed as detects or non-detects while BDE-183 was nearly undetectable (98.6% non-detect).

2.5. Chemical analysis of phthalate metabolites in urine

Urine samples were assayed for a total of 24 phthalate metabolites (Table S1) by the Centre de Toxicologie du Québec (CTQ) of the Institut National de Santé Publique du Québec (INSPQ) as described previously