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Couples' urinary concentrations of benzophenone-type ultraviolet filters and the secondary sex ratio

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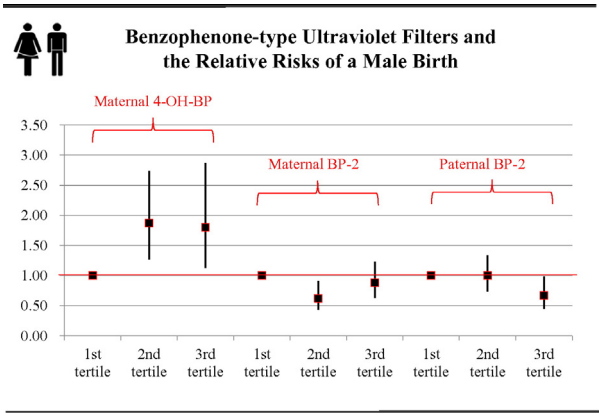
HIGHLIGHTS

- Several environmental chemicals are associated with the secondary sex ratio.
- Maternal urinary concentration of 4-OH-BP was associated with male excess of births.
- Maternal and paternal urinary BP-2 concentrations were associated with female excess.
- These findings need future corroboration, given the exploratory design of this study.

GRAPHICAL ABSTRACT



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ABSTRACT

The secondary sex ratio (SSR), defined as the ratio of males to females at birth, has been investigated in relation to endocrine disruptors to search for environmental toxicants perturbing human sex selection. Benzophenone (BP)-type ultraviolet (UV) filters, which are used in sunscreens and personal care products, have been reported to exert estrogenic and anti-androgenic activities. This study aimed to evaluate the association between maternal, paternal, and couple urinary concentrations of BP-type UV filters and the SSR, given the absence of previous investigation. The study cohort comprised 220 couples who were enrolled in the Longitudinal Investigation of Fertility and the Environment (LIFE) Study between 2005 and 2009 prior to conception and who had a singleton birth during the follow-up period. Couples' urinary concentrations of five BP-type UV filters (ng/mL) were measured using triple-quadrupole tandem mass spectrometry: 2,4-dihydroxybenzophenone (BP-1), 2,2′,4,4′-tetrahydroxybenzophenone (BP-2), 2-hydroxy-4-methoxybenzophenone (BP-3), 2,2′-dihydroxy-4-methoxybenzophenone (BP-8), and 4-hydroxybenzophenone (4-OH-BP). Modified Poisson regression models were used to estimate the relative risks (RRs) of a male birth for each BP-type UV filter, after adjusting for potential confounders. When maternal and paternal urinary BP-type UV filter concentrations were modeled jointly, both maternal BP-2 (2nd vs 1st tertile, RR, 0.62, 95% confidence interval [CI], 0.43–0.91) and paternal BP-2 (3rd vs 1st tertile, RR, 0.67, 95% CI, 0.45–0.99; *p*-trend, 0.04) were significantly associated with an excess of

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female births. Contrarily, maternal 4-OH-BP was significantly associated with an excess of male births (2nd vs 1st tertile, RR, 1.87, 95% CI, 1.27–2.74; 3rd vs 1st tertile, RR, 1.80, 95% CI, 1.13–2.87; *p*-trend, 0.02). Our findings provide the first evidence suggesting that BP-type UV filters may affect the SSR. However, future corroboration is needed, given the exploratory design of this study.

1. Introduction

While the primary sex ratio is defined as the ratio of males to females at conception, the secondary sex ratio (SSR) is defined as the ratio of males to females at birth (Buck Louis and Platt, 2011). Due to difficulties in investigating conception at the population level (Orzack et al., 2015), the SSR, as an indicator of population health and fertility, has been explored in relation to endocrine disruptors to search for environmental toxicants perturbing human sex selection (Terrell et al., 2011). Deviations from an expected SSR, which is thought to range from 1.05 to 1.07 (Central Intelligence Agency; Mathews and Hamilton, 2005), can provide clues about underlying changes in population-wide environmental factors (Davis et al., 2007). Diverse classes of chemicals suspected of affecting endocrine function have been examined in relation to various reproductive and developmental outcomes including the SSR in humans. Specifically, persistent chemicals, which can accumulate in the environment and human body, have been reported to be associated with alterations in the SSR, exampled by chemicals such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Mocarelli et al., 2000), polychlorinated biphenyls (PCBs) (Nieminen et al., 2013), and perfluoroalkyl and polyfluoroalkyl substances (PFASs) (Bae et al., 2015b). Although inconclusive with limited evidence, parental exposure to non-persistent chemicals with a relatively short half-life and low bioaccumulative potential, such as bisphenol A (BPA) and phthalates, has been also reported to be associated with an excess of male or female births (Bae et al., 2015a).

Sunscreen agents are routinely applied to the skin by a large percentage of contemporary populations to provide protection against ultraviolet (UV) radiation, which is a well-known cause of skin photoaging and photocarcinogenesis (Pillai et al., 2005; Saraiya et al., 2004). These agents commonly contain a combination of several organic and inorganic UV filters for broad-spectrum protection against different types of UV light (Villalobos-Hernández and Müller-Goymann, 2006). Due to their photoallergic properties, organic or chemical UV filters such as para-aminobenzoic acid (PABA) and benzophenones (BPs) were first targeted by public health concern, while inorganic or mineral UV filters such as zinc oxide and titanium dioxide were then at the heart of scientific debates particularly because of their nanometric size (Gilbert et al., 2013). Along with acute toxic effects of sunscreen agents, interest in their chronic toxicity including reproductive and developmental effects has been growing, in light of their systemic absorption after topical application (Janjua et al., 2008; Jiang et al., 1999; Maier and Korting, 2005).

Although PABA was introduced as one of the first organic UV filters (Mackie and Mackie, 1999), 2-hydroxy-4-methoxybenzophenone (BP-3), also known as oxybenzone, is one of the most commonly-used chemical components in sunscreen formulations (Careghini et al., 2015; Kim and Choi, 2014; Maier and Korting, 2005). Indeed, different types of BP compounds from 2,4-dihydroxybenzophenone (BP-1) to 2-hydroxy-4-octyloxybenzophenone (BP-12) have been used in a variety of personal care products including sunscreens and cosmetics as well as plastic surface coatings for food packaging, because of their UV absorption properties (Kawamura et al., 2003; Liao and Kannan, 2014; Park et al., 2013; Schlecht et al., 2006). With diverse sources for human exposure, widespread occurrence of BP-3 as well as its metabolic derivatives such as BP-1, 2,2′,4,4′-tetrahydroxybenzophenone (BP-2), 2,2′-dihydroxy-4-methoxybenzophenone (BP-8), and 4-hydroxybenzophenone (4-OH-BP) has been reported in many countries including the United States (Calafat et al., 2008; Philippat et al., 2015; Wang and Kannan, 2013; Wolff et al., 2008), China (Wang and Kannan, 2013; Zhang et al., 2013), and some European countries (Asimakopoulos et al., 2014; Philippat et al., 2012; Schlumpf et al., 2010). The reported urinary concentrations of BP-type UV filters, as commonly-used biomarkers of exposure to these chemicals, varied markedly across populations, with relatively scanty data on these chemical concentrations in other samples such as blood (Zhang et al., 2013) and breast milk (Schlumpf et al., 2010).

BP-type UV filters are an emerging class of endocrine disruptors, with various documented hormonal activities in vitro and in vivo. Specifically, BP-3 and its metabolic derivatives such as BP-1, BP-2, BP-8, and 4-OH-BP have been shown to elicit estrogenic activity in a variety of in vitro assays (Kawamura et al., 2003, 2005; Kunz and Fent, 2006; Morohoshi et al., 2005; Nakagawa and Suzuki, 2002; Nakagawa et al., 2000; Ogawa et al., 2006; Schlumpf et al., 2001, 2004; Schreurs et al., 2002, 2005; Suzuki et al., 2005). Of note, the estrogenic potency of some metabolic derivatives of BP-3 including BP-1, BP-2, and 4-OH-BP was found to be higher than that of their parent compound, BP-3 (Kunz and Fent, 2006; Morohoshi et al., 2005). In acute in vivo models, the estrogenic activity of BP-type UV filters was confirmed by increased uterine weight following BP-3 (Schlumpf et al., 2001, 2004), BP-1 (Schlumpf et al., 2004), BP-2 (Schlumpf et al., 2004; Yamasaki et al., 2003), or 4-OH-BP (Nakagawa and Tayama, 2001; Yamasaki et al., 2003) exposure in immature rats, although the uterotrophic effect in immature rats conflicted with unchanged uterine weight following BP-3 exposure in oophorectomized rats (Schlecht et al., 2004; Suzuki et al., 2005). Another reported hormonal activity of BP-3 and its metabolic derivatives such as BP-1, BP-2, BP-8, and 4-OH-BP is in vitro anti-androgenic activity (Kawamura et al., 2005; Kunz and Fent, 2006; Ma et al., 2003; Schlumpf et al., 2004; Schreurs et al., 2005; Suzuki et al., 2005). Furthermore, some (Kunz and Fent, 2006; Morohoshi et al., 2005) but not all (Schreurs et al., 2002) experimental studies demonstrated that BP-3 exerted anti-estrogenic activity in vitro. Additionally, in vitro antagonistic action on human progesterone receptor (PR) was noted for BP-3 (Schreurs et al., 2005). BP-2 was also found to be androgenic in vitro, with the androgenic potency approximately 30,000-times less than that of 4,5-dihydrotestosterone (DHT) (Kunz and Fent, 2006).

Some (French, 1992; Hsieh et al., 2007; Weisbrod et al., 2007) but not all (Blüthgen et al., 2012) animal studies have shown that select BP-type UV filters may result in alterations in the reproductive system. Moreover, although preliminary in nature, results from recent human studies suggest that BP-type UV filters may be associated with couple fecundity (Buck Louis et al., 2014), semen quality (Buck Louis et al., 2015), birth outcomes (Wolff et al., 2008), and some estrogen-dependent gynecologic diseases such as uterine leiomyoma (Pollack et al., 2015) and endometriosis (Kunisue et al., 2012). In light of these emerging data on the reproductive and developmental toxicity of BP-type UV filters and the absence of previous investigation focusing on the SSR, we explored the association between maternal, paternal, and couple urinary concentrations of five BP-type UV filters (i.e., BP-3 and its metabolic derivatives, BP-1, BP-2, BP-8, and 4-OH-BP) and the SSR in a population-based preconception cohort.

2. Methods

2.1. Study population

The Longitudinal Investigation of Fertility and the Environment (LIFE) Study is a prospective cohort study designed to assess