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Major benzophenone concentrations and influence of food consumption among the general population in Korea, and the association with oxidative stress biomarker

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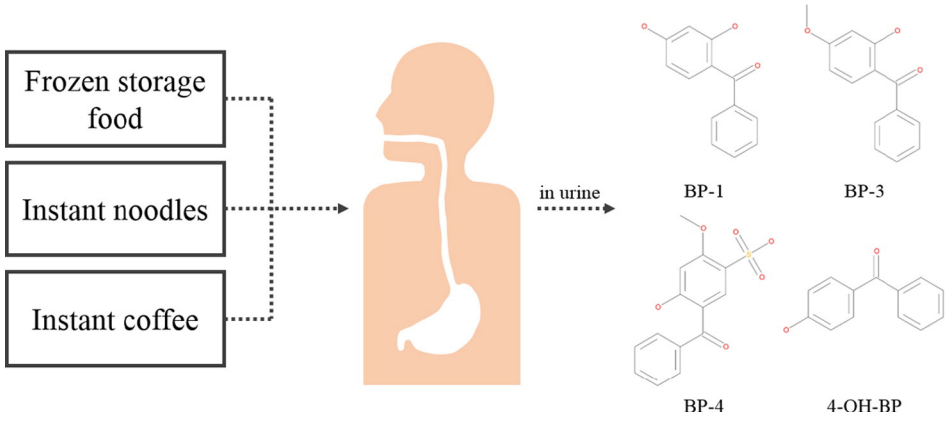
HIGHLIGHTS

- Benzophenone (BP) levels were higher in younger cosmetic users and leaner women.
- Intake of frozen storage food was significantly correlated with urinary BP levels.
- Association between urinary BP levels and food consumption was sex-dependent.
- No significant correlation was observed between the level of BPs and MDA.

GRAPHICAL ABSTRACT



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ABSTRACT

Benzophenones (BPs) have been used as sunscreen agents and as ultraviolet stabilizers in plastic surface coatings for food packaging. However, few studies have been performed to examine the level of human exposure to BPs and the potential sources of such exposure. We evaluated the exposure levels to six major BPs (BP-1, BP-2, BP-3, BP-4, BP-8, and 4-hydroxybenzophenone (4-OH-BP)) among the adult population in two cities in Korea, and investigated the potential dietary sources of the BPs. Urinary levels of malondialdehyde (MDA) as an oxidative stress biomarker as well as their association with the levels of BPs were also analyzed. Among the six BPs analyzed, 4-OH-BP, BP-1, BP-3, and BP-4 were detected in 77%, 49%, 27%, and 21% of the population, respectively. BP concentrations were relatively higher in younger (people in their 20s and 30s) cosmetic users and leaner women. Even after the adjustment of age, body mass index, and cosmetic use, the consumption of frozen storage food, instant noodles, and instant coffee was significantly correlated with urinary BPs, and these associations were sex-dependent. No significant correlation was observed between the levels of BPs and levels of MDA. The results of the present study will be useful for developing plans of public health management of BPs.

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1. Introduction

Benzophenones (BPs) have been commonly used as sunscreen agents in cosmetic products and as ultraviolet (UV) stabilizers in plastic surface coatings for food packaging (Suzuki et al., 2005). Among the family of BPs, BP-3 (2-hydroxy-4-methoxybenzophenone) is the most widely used compound for prevention of photo-degradation (Zhang et al., 2013). These chemicals can be present in food packaging materials as a residue from UV-cured inks and lacquers used to print on the packaging (Jung et al., 2013). Considering the migration of printing ink ingredients from packaging into foodstuffs, the Ministry of Food and Drug Safety (MFDS) in Korea reported a specific migration limit (SML) of 0.6 mg/L for BPs (MFDS, 2015). In the European Union, there is specific legislation for plastics that come into contact with food (directive 2002/72/EC), which sets a SML of 0.6 mg/kg for BPs (European Union, 2002).

Several studies have reported a variety of adverse health effects associated with exposure to BP derivatives. BP-3 can act as a weak estrogen agonist and strong androgen antagonist (Ma et al., 2003; Schlumpf et al., 2001; Schreurs et al., 2005; Suzuki et al., 2005), and is associated with the estrogen-mediated disease endometriosis in women (Kunisue et al., 2012). Some of the precursors and metabolites of BP-3, e.g., BP-1 (2.4-dihydroxybenzophenone), BP-2 (2.2′,4,4′-tetrahydroxybenzophenone), and 4-OH-BP (4-hydroxybenzophenone) were found to possess greater estrogenic activity than BP-3 (Kawamura et al., 2003, 2005; Nakagawa and Suzuki, 2002; Suzuki et al., 2005). Maternal BP-3 exposure was associated with Hirschsprung's disease in their offspring (Huo et al., 2016).

Because potential health consequences of BPs were suspected in the general population, several reports were made on urinary BP levels in people around the world who are exposed to BPs non-occupationally (Kim and Choi, 2014). BP-3 was found in >95% of urine samples collected from the U.S. general population, with concentrations ranging from 0.4 to 21,700 ng/mL (Calafat et al., 2008). Sex-dependent differences in urinary BP levels have been frequently reported elsewhere; females showed higher levels of urinary BP concentration than males (Heffernan et al., 2015; Kunisue et al., 2012; Moos et al., 2014; Zhang et al., 2013). Measured BP-3 concentrations in children were generally lower than in the adult population (Calafat et al., 2008; Frederiksen et al., 2013; Wang and Kannan, 2013). Information on BP derivatives in Korean adults is very limited; only three studies have reported the urinary concentrations of BP-1, BP-3, and 4-OH-BP in the Korean adult population (Ko et al., 2015; MFDS, 2014; Oh et al., 2013).

In relation to human exposure to BPs, cosmetics applied to human skin have been considered one of the major exposure pathways for BPs. A couple of studies have suggested that BP-3 can penetrate human skin (Janjua et al., 2004; Jiang et al., 1999), and a significant relationship was observed between urinary BP-3 concentrations and the application of personal care products that contain UV filters (Ko et al., 2015; Zamoiski et al., 2015). Although dermal exposure to sunscreen agents has been considered as potential sources of BP exposure by a number of studies (Philippat et al., 2015; Zamoiski et al., 2015), including our parallel study (Ko et al., 2015), other routes of human exposure to BPs have not yet been demonstrated. For example, migration of printing ink ingredients from the outside of the food packaging material to the inside, can be a potential source of BPs in humans as well (Anderson and Castle, 2003; Johns et al., 2000).

Lipid peroxidation is a process generated by the effect of free radicals in an organism, and an increase in free radicals causes overproduction of malondialdehyde (MDA). Therefore, MDA levels are commonly used as a marker of oxidative stress (Gawel et al., 2004). Several human studies have explored exposure to endocrine disrupting chemicals in relation to oxidative stress, as these processes are potential important mediators of cancer, pregnancy outcome, and cardiovascular disease (Watkins et al., 2015). For example, 2.4-dichlorophenol, parabens, phthalates, and bisphenol A have been associated with a number of biomarkers of oxidative stress in humans (Bukowska, 2003; Ji et al., 2010; Kang et al., 2013; Yang et al., 2009). In *in vitro* studies, BP-3 has been associated with markers of oxidative stress (Gao et al., 2013; Kato et al., 2006). However little is known about the relationship between benzophenone and biomarkers of oxidative stress in urine samples.

In the present study, we measured the levels of six major BPs in adults in Seoul and Gyeonggi, Korea, and investigated whether diet played a role. The relationship between the urinary MDA concentration as a biomarker of oxidative stress and the urinary BP concentration was also evaluated. The results of this study will be useful in developing management plans for major BPs in the general human population.

2. Materials and methods

2.1. Study population

A study population, all of whom were aged 19 and older, was recruited from Seoul and Gyeonggi province in the Korean peninsula between July and August 2014. Male and female participants were sorted into one of five age categories (19–29 years, 30–39 years, 40–49 years, 50–59 years, and 60 years and older). A total of 200 subjects were recruited, however, 23 individuals were excluded from analysis because parts of the relevant information were missing ($n = 177$, 87 males and 90 females). The written statements of informed constant were obtained from all participants. The present study was approved by the Institutional Review Board of Eulji University (Gyeonggi, Korea).

2.2. Questionnaire survey and urine sampling

An extensive questionnaire was developed to gather information on the dietary patterns, application of cosmetics, and demographic details of the participants. One-on-one interviews by a trained interviewer were conducted at the time of urine sampling. To assess the influence of dietary factors, the average frequency of consumption for a given food item (retort food, frozen storage food, chilled storage food, ketchup and mayonnaise, popcorn and nachos, pizza, chicken, potato snacks and French fries, biscuits, cereal, instant coffee, tea packed with tea back, instant noodles, ice cream, takeout food) and the serving size of food items were investigated. The average frequency of cosmetic use over a defined period of time (e.g., day, week, or month) was asked. The cosmetics included sunscreen, skin care products, functional cosmetics (e.g., whitening and anti-wrinkle cosmetics), makeup base (e.g., BB and CC cream), skin-colored makeup (e.g., foundation and powder), lip cosmetics, eye cosmetics, color cosmetics (e.g., highlighters and blush), hair care products, perfume, and nail products. Demographic information (age, sex, weight, and height) was also collected. The urine samples were collected and stored at −80 °C prior to analysis.

2.3. Sample preparation and analysis of BPs

Human urine samples were analyzed for six BPs: BP-1 (purity 96%), BP-2 (98%), BP-3 (95%), BP-4 (4-hydroxy-2-methoxy-s(oxophenylmethyl)benzenesulfonic acid; 95%), BP-8 (2.2′-dihydroxy-4-methoxybenzophenone; 98%), and 4-OH-BP (97%), according to the methods outlined in Ko et al. (2015). Physicochemical characteristics of the analyzed compounds are shown in Table S1. All urine samples were deconjugated by enzymatic hydrolysis, and the total (i.e., free plus conjugated) concentrations of benzophenones were determined by the isotope dilution method. Briefly, 100 μL of internal standard (10 mg/L of bisphenol A-d_{16}) was spiked into 1 mL of urine in a 2 mL glass vial. Urine samples were enzymatically deconjugated by the addition of 1 mL of 0.1 M ammonium acetate (pH 5.0), which contained 46 units of 50 μL β-glucuronidase/sulfatase (Type HP-2, from *Helix pomatia*, ≥100,000 units/mL glucuronidase and ≤7,500 units/mL sulfatase (Sigma-Aldrich, St. Louis, MA, USA)). After incubation at 37 °C for 4 h, the digested sample (1 mL) was loaded onto the C18 Sep-Pak cartridge