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Ten-year trends in urinary concentrations of triclosan and benzophenone-3 in the general U.S. population from 2003 to 2012

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ABSTRACT

Despite their popular use and emerging evidences of adverse health effects, consequent trends in population level triclosan and benzophenone-3 exposure have been poorly evaluated. Therefore, we examined temporal trends of urinary triclosan and benzophenone-3 concentration in the general U.S. population by combining five cycles of National Health and Nutritional Examination Survey (NHANES, 2003–2012) data. We calculated percent changes and the least square geometric means (LSGMs) of urinary triclosan and benzophenone-3 concentration from 10,232 participants by using multivariable regression models. As a result, LSGM concentration of urinary triclosan and benzophenone-3 did not show statistically significant changes over the study period. [Percent change (95% CI): Triclosan, −7.35% (−20.86, 8.47); Benzophenone-3, 7.08% (−27.88, 58.99)] However, we found decreasing trend of urinary triclosan concentration and increasing trend of urinary benzophenone-3 concentration since 2005–2006. Socio-demographic factors which affected urinary concentration of triclosan and benzophenone-3 persisted throughout 10 year study period. Highest income group showed higher level of urinary triclosan and benzophenone-3 concentration. Overall concentration of benzophenone-3 was higher in female than in male, and higher in non-Hispanic Whites than any other races/ethnicities.

1. Introduction

Triclosan (2,4,4′-Trichloro-2′-hydroxy-diphenylether) and Benzophenone-3 (BP3, 2-hydroxy-4-methoxybenzophenone) are popular chemicals which are used in various consumer products in everyday life. Although they do not share similar chemical structure or properties, triclosan and BP3 has been highly detected in general U.S. population and their major exposure sources are believe to be personal care products. By analyzing 2003–2004 National Health and Nutrition Examination Surveys (NHANES) data, triclosan and BP3 were detected in 74.6% and 96.8% of the urine samples and concentration was differed by socio-demographic factors (Calafat et al., 2008a,b). For instance, urinary concentration of triclosan peak around the third decade of life and people in the highest income group showed higher triclosan concentration than low income groups. In case of BP3, women and non-Hispanic White showed higher urinary concentration than men and other race/ethnicities.

Triclosan is a broad-spectrum phenolic biocide, which is used for preservative, antibacterial, and antifungal purposes. Since its first registration with the Environmental Protection Agency (EPA) in 1969, triclosan has been used in variety of personal care and household products, such as hand washing soaps, toothpastes, cosmetics, kitchen ware, toys, and medical devices (Dann and Hontela, 2011). Human exposure of triclosan mainly occurs by oral and dermal route (Moss et al., 2000; Sandborgh-Englund et al., 2006), and metabolized by glucuronidation and sulfation at liver or during the passage through the skin (Rodricks et al., 2010). Administered triclosan is excreted by urine and feces with mean elimination half-life of 10–20 h for oral exposure and 1.4 days for dermal exposure (Rodricks et al., 2010).

Recently, there are numerous health and safety concerns regarding triclosan's endocrine-disrupting properties and antibiotic-resistant bacteria formation. In studies with rats, exposure to triclosan decreased levels of thyroid hormones (Crofton et al., 2007; Zorrilla et al., 2009), androgen hormones, and sperm

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counts (Kumar et al., 2009). In addition, there is emerging evidence of hormone-disturbing effects of triclosan from human studies. In studies with NHANES, researchers found associations between triclosan exposure and altered thyroid hormone levels (Koeppe et al., 2013), body mass index, and waist circumference (Lankester et al., 2013; Li et al., 2015). In studies with Norwegian children and NHANES, triclosan concentrations were associated with allergic sensitization to inhalant and seasonal allergen and the diagnosis of allergy and hay fever (Bertelsen et al., 2013; Clayton et al., 2010). Furthermore, several bacterial species with reduced susceptibility to triclosan showed cross-resistance to other antibiotics (Braoudaki and Hilton, 2004; Cookson et al., 1991; Randall et al., 2004).

Triclosan may affect homeostasis of the ecosystem by its biochemical properties and frequent use of products containing triclosan among the public. As most triclosan-containing soap and cosmetics wash down drains and enter waterways, U.S. geological studies in 1999–2000 found triclosan in 57.6% of 139 American streams (Kolpin et al., 2002). Although wastewater treatment plant removes over 90% of triclosan, triclosan persist through treatment and discharged into surface water. Therefore studies using sediment samples of freshwater lakes across Minnesota found that all tested lakes contained triclosan and chlorinated triclosan derivatives in sediments and concentration has been increased since the 1960s. A study also revealed potential biochemical reactions, which might transform triclosan into the hazardous gas chloroform and into toxic dioxin compounds in oceans and freshwater lakes (Anger et al., 2013).

BP3 is an organic compound commonly used for UV filters in sunscreens (Gonzalez et al., 2006). Since its approval by the FDA in the early 1980s, BP3 has been widely used in products, such as sunscreens, hair sprays, and cosmetics, to prevent potential damage from sunlight exposure. Human exposure to BP3 mainly occurs by applying BP3 containing sunscreen or consumer products on the skin (Gonzalez et al., 2006; Sarveiya et al., 2004). Although metabolic transformation pathways and products are unclear, BP3 is believed to be metabolized by demethylation in humans and mainly excreted by the urines (Wang and Kannan, 2013). After the dermal application of the recommended amount of a commercially available sunscreen by eleven volunteers, approximately 0.4% of the applied amount of BP3 was detected in urine over 48 h (Gustavsson Gonzalez et al., 2002).

Recently many *in vivo* and *in vitro* studies have indicated potential endocrine-disrupting effects of BP3 such as disturbance of estrogenic signaling, androgenic activity, and the hypothalamic pituitary axis (Krause et al., 2012). In studies assessing associations between prenatal BP3 exposure and human offspring size, maternal gestational urinary concentrations of BP3 were positively associated with body weight and head circumference at birth in boys, but negatively associated with birth weights in girls (Philippat et al., 2012; Wolff et al., 2008). However, in two clinical trials with similar design, researchers couldn't ascertain if changes in reproductive or thyroid hormone levels are related to BP3 exposure(Janjua et al., 2007, 2004). In a single blind crossover studies conducted for 2 consecutive weeks with 1 control week and 1 treatment week, 15 young men and 17 postmenopausal women were instructed to apply basic cream with or without sunscreen mixture (BP3, 3-4-methylbenzylidene and octylmethoxycinnamate) for 4 days each. Researchers only found minor difference in several hormone levels between control and treatment week and these differences did not seem to be associated with BP3 exposure (Janjua et al., 2007, 2004).

Despite popular use and emerging evidence of potential adverse health effects of triclosan and BP3, temporal trends in population-level environmental exposure have never been evaluated. Evaluating long term temporal trend of nationally representative human chemical concentrations could be a valuable instrument for finding factors associated with human exposure, depicting susceptible exposure groups, and deciding direction for future legislative movements. Therefore, we used NHANES data to analyze temporal patterns of triclosan and BP3 exposure levels in the U.S. population from 2003 to 2012. We also tried to assess whether socio-demographic factors (sex, age, race/ethnicity, or household income) which affected chemical concentration at 2003–2004 NHANES data persisted throughout 10 year study periods.

2. Material and methods

2.1. Study population

We used data from the 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012 cycles of NHANES, a nationally representative survey and physical examination of the civilian, non-institutionalized U.S. population conducted by the Centers of Disease control and Prevention (CDC). Among a total of 50,912 participants throughout all the five cycles, we identified participants with triclosan and BP3 measurements (n = 12,907). After excluding participants with missing urinary creatinine level data (n = 5) and information on household income (n = 937), and participants who did not self-identify as non-Hispanic White, non-Hispanic Black, or Mexican-American (n = 1944), a total of 10,232 participants were used in the final analysis. The National Centers for Health Statistics Institutional Review Board reviewed and approved the study protocol. Informed consent was obtained from all participants.

2.2. Urinary triclosan and benzophenone-3

Single spot urine samples were collected in the Mobile Examination Center and stored at −20 °C until shipped to the CDC's National Center for Environmental Health in Atlanta, GA for analysis. Total (free plus conjugated) concentrations of triclosan and BP3 were measured in urine by online solid-phase extractions coupled to high-performance liquid chromatography-tandem mass spectrometry, as described in detail elsewhere (Ye et al., 2005). Former studies revealed that urinary concentrations of triclosan and BP3 can be used as biomarkers of exposure (Calafat et al., 2008a,b).

The limits of detection (LOD) for triclosan and BP3 varied across study cycles. Therefore, to conduct reasonable analyses across cycles, we assumed a maximal value among LODs for the LOD of triclosan (2.3 ng/mL) and BP3 (0.4 ng/mL) and substituted value below the LOD with value of the LOD divided by the square root of 2 (Table 1). This produces reasonably non-biased means and standard deviations (Hornung and Reed, 1990).

2.3. Statistical analysis

Concentrations of triclosan and BP3 were natural log-transformed to approximate a normal distribution. To calculate the percent change and the least square geometric means (LSGMs) of triclosan and BP3 concentration by NHANES cycles, we used multivariable regression models. By using concentrations of triclosan or BP3 as the outcome variables and NHANES sampling cycles and urinary creatinine concentration as independent variables, we calculated concentration percent changes throughout the NHANES study cycles. We used the 2003–2004 cycle as reference group. Urinary creatinine was natural log-transformed to approximate a normal distribution and included in the model to adjust for urine dilution (Barr et al., 2005).

LSGMs are the cycle-specific mean concentrations of triclosan

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