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Risk assessment based on urinary bisphenol A levels in the general Korean population

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ABSTRACT

Bisphenol A (BPA) is a high-volume industrial chemical used in the global production of polycarbonate plastics and epoxy resins, which are used in food and drink containers, such as tableware (plates and mugs). Due to its broad applications, BPA has been detected in human blood, urine and breast milk as well as environmental substances, including water, indoor and outdoor air, and dust. Indeed, exposure to high concentrations of BPA can result in a variety of harmful effects, including reproductive toxicity, through a mechanism of endocrine disruption. Our comparison of reported BPA urinary concentrations among different countries revealed that exposures in Korea may be higher than those in other Asian countries and North America, but lower than or similar to those in European countries. The current study included a total of 2044 eligible subjects of all ages. The subjects were evenly divided between males and females (48.58% and 51.42%, respectively). The geometric mean (GM) of pre-adjusted (adjusted) urinary BPA concentrations was 1.83 μg/L (2.01 μg/g creatinine) for subjects of all ages, and there was no statistically difference in BPA concentrations between males (1.90 μg/L, 1.87 μg/g creatinine) and females (1.76 μg/L, 2.16 μg/g creatinine). Multiple regression analysis revealed only one positive association between creatinine pre-adjusted urinary BPA concentration and age ($\beta = -0.0868$, $p < 0.001$). The 95th percentile levels of 24-hour recall (HR), food frequency questionnaires (FFQ) and estimated daily intake (EDI) through urinary BPA concentrations were 0.14, 0.13, and 0.22 μg/kg bw/day, respectively. According to the Ministry of Food and Drug Safety (MFDS), a tolerable daily intake (*t*DI) of 20 μg/kg bw/day was established for BPA from the available toxicological data. Recently, the European Food Safety Authority (EFSA) established a temporary TDI of 4 μg/kg bw/day based on current toxicological data. By comparing these TDIs with subjects' exposure, we conclude that there are no health concerns for any age group as a result of current levels of dietary exposure to BPA.

1. Introduction

Bisphenol A (BPA; 2,2′-bis[4-hydroxyphenyl]propane) is a high-volume industrial chemical used in the global production of polycarbonate plastics and epoxy resins. Approximately six million tons of BPA are produced per year and are used in food and drink containers, such as tableware (plates and mugs) and microwave ovenware (Vandenberg et al., 2012). These applications result in the exposure of consumers, including infants, to BPA through the diet. In humans, the routes of exposure to BPA are known to be via diet, inhalation of household dust, and dermal exposure (Geens et al., 2012). Oral exposure from food is generally considered the major source of BPA exposure for all age groups among the population without occupational exposure (Cao et al., 2010; Geens

Abbreviations: ANSES, French Agency for Food, Environmental and Occupational Health & Safety; BMD, Benchmark dose; BMDL, the 95% Lower confidence limit of benchmark dose; BPA, Bisphenol A; CHMS, Canadian health measures survey; EDI, Estimated daily intake; EFSA, European food safety authority; HbGV, Health-based guidance value; HED, Human equivalent dose; FAO, Food and Agriculture Organization of the United Nations; FFQ, Food frequency questionnaire; GerES IV, German Environmental Survey for Children; GM, Geometric mean; JECFA, Joint FAO/WHO Expert Committee on Food Additives; KRIEFS, Korean research project on the integrated exposure assessment to hazardous materials for food safety; LOAEL, Lowest observed adverse effect level; LOD, Limit of detection; MFDS, Ministry of Food and Drug Safety; NHANES, National Health and Nutrition Examination Survey; NOAEL, No observed adverse effect level; PBPK, Physiologically-based pharmacokinetic; POD, Point of departure; TDI, Tolerable daily intake; UF, Uncertainty factor; UNEP, United Nations Environment Programme; WHO, World Health Organization; 24HR, 24-hour recall

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et al., 2012; Liao and Kannan, 2011).

According to multiple toxicokinetic studies on BPA in humans, BPA is almost completely excreted in urine as the conjugated form within 24 h after exposure (Teeguarden et al., 2011; Völkel et al., 2008). Long-term daily intake of BPA leads to steady-state BPA concentrations in the ng/mL range in human urine samples (Welshons et al., 2006). Thus, total urinary BPA concentration (conjugated and unconjugated forms) is the biomarker of choice to estimate BPA exposure. The World Health Organization (WHO) reported that, while the levels of exposure vary somewhat across age groups, the ranges of the estimated exposure to BPA by diet and the extrapolated exposure based on urinary BPA concentrations have a mean of 0.01–2.4 μg/kg bw/day (95th percentile, 0.1–4.5 μg/kg bw/day) and median of 0.02–0.12 μg/kg bw/day (95th percentile, 0.27–1.61 μg/kg bw/day), respectively (WHO, 2011).

Many studies have reported the adverse effects of BPA, including reproductive and developmental, neurological and neurodevelopmental, immune, cardiovascular, and metabolic effects (ANSES, 2013; EFSA, 2015b; USEPA, 1998; WHO, 2011). In particular, numerous studies have reported the endocrine effects of BPA, noting that it can adversely affect physical, neurological, and behavioral development (Beausoleil et al., 2013; Galloway et al., 2010; Vandenberg et al., 2012). Recently, many studies have reported a significant association between urinary BPA concentration and obesity (Andra and Makris, 2015; Braun et al., 2014; Oppeneer and Robien, 2015). In our previous study, we have also observed a positive association between urinary BPA concentration and waist circumference in Korean adults (Ko et al., 2014).

International scientific committees such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), regional scientific committees such as those of the European Union, and national regulatory agencies generally use the safety factor approach for establishing acceptable or tolerable intakes of substances that exhibit thresholds of toxicity (Herrman and Younes, 1999). In the analyses of JECFA and the European Food Safety Authority (EFSA), BPA has consistently been found to cause a number of adverse health effects at doses of 50 mg/kg bw/day and above in rodents, including fetal deaths, decreased litter size or decreased number of live pups per litter, and reduced fetal or postnatal growth in rats and mice. According to EFSA (2006), a dose of 5 mg/kg bw/day has been identified as a no observed adverse effect level (NOAEL). A tolerable daily intake (*t*DI) of 50 μg/kg bw/day was derived using an uncertainty factor (UF) of 100 to account for interspecies variability of 10 and intraspecies variability of 10. In South Korea, the Ministry of Food and Drug Safety (MFDS) also suggested a TDI of 50 μg/kg bw/day for the South Korean population (Choi et al., 2010). Although there was weak evidence according to statistical and methodological approaches, a number of studies reported adverse effects of BPA below the NOAEL of 5 mg/kg bw/day, which was the point of departure (POD) of the TDI. Endocrine disruptors often follow non-monotonic dose-response curves and can exhibit greater effects at lower doses (Beausoleil et al., 2013; Vandenberg et al., 2012; Wolstenholme et al., 2011). Many studies have also reported that BPA causes adverse effects at lower doses than the TDI. As a result, in 2015, EFSA performed a new hazard characterization of BPA, based on a comprehensive evaluation of recent toxicity data, and set a temporary tolerable daily intake (t-TDI) of 4 μg/kg bw/day for BPA by applying a UF of 150 to the human equivalent dose (HED) of 609 μg/kg bw/day (EFSA, 2015b).

Currently, there are increasing concerns about the low dose effects of BPA. It is important to know the level of BPA exposure and whether or not adverse health effects result from this level of exposure. In the present study, we retrieved data on urinary total BPA levels for North America, Europe, and Asia from scientific journals and national health survey websites. We compared urinary BPA concentrations of the general Korean population to those for each of the other countries. We also re-evaluated the Korean TDI for BPA and performed exposure assessment for BPA by using daily intake through food and estimated daily intake (EDI) through urinary concentrations.

2. Methods

2.1. Literature search

To compare urinary BPA levels among the countries, we searched through the medical literature database PubMed by combining the keywords bisphenol A, BPA, biomonitoring, epidemiology, cohort, case-control and cross section. We also retrieved data through the websites of health and safety authorities and national health surveys such as the US Environmental Protection Agency (EPA), Health Canada, and EFSA.

To establish a health-based guidance value (HbGV) for BPA, we searched toxicological data through databases such as PubMed and TOXLINE, and risk assessment documents through the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), EFSA, and the US EPA.

2.2. Design and study subjects

This study was based on data obtained by the Korean Research Project on Integrated Exposure Assessment to Hazardous Materials for Food Safety (KRIEFS) to analyze detailed BPA exposure through urinary BPA. The KRIEFS was a nationwide study performed by the MFDS from 2010 to 2012 to evaluate integrated exposure to hazardous materials through the intake of foods, oriental medicine, and health supplements (Lim et al., 2012). The study protocol was approved by the Human Investigation Review Board at Dankook University College of Medicine. Informed consent was obtained from all subjects prior to participation. The survey was categorized based on the subjects' age group (i.e., adult, child and adolescent, and infants). For adults, a minimum number of samples were allotted according to region, gender, and age. The adult samples were extracted by a method of square root percentage quota based on a distribution ratio of the population. For the child and adolescent group and the infant group, the survey employed a cluster sampling method that centered on schools or organizations in three of the four main areas of various cities in Korea.

The subjects (n=2044) were individually interviewed by trained technicians using standard protocols. A questionnaire was developed for this study that included questions on age, education, income, smoking status, alcohol consumption, and dietary intake. Subject age groups ranged from 1 to 72 months (infant), 7–18 years (child and adolescent), and 19 years and above (adult). The education status of the subjects was categorized as less than high school, high school, and greater than high school. Household income was categorized as less than $2,000, $2,000–$3.000, $3,000–$4,000 and more than $4,000. Smoking status was categorized as never, former, and current. Alcohol consumption was categorized as less than 1 time per week, 1 time per week, 2–3 times per week and more than 3 times per week.

2.3. Analysis of BPA

2.3.1. Urine

Twelve hr urine samples that were collected between 7:00 pm and 9:00 am and included the first morning void were analyzed in this study. A urine sample (1 mL) was buffered with 30 μL of 2 M sodium acetate (pH 5.0), followed by the addition of 1 mL of 0.5 μg/mL BPA (RING-13C12, 99%; Cambridge Isotope Lab, Inc.,