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Biological Monitoring of Bisphenol A in a Korean Population

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Abstract. To conduct proper biological monitoring of environmental exposure to bisphenol A (BPA), the variation in host susceptibility need to be investigated. For this purpose, we studied effects of genetic polymorphism in sulfotransferase (*SULT*) *1A1* on urinary BPA, a biomarker for BPA exposure, in 73 Koreans (male, 34; female, 39; age, 48.9 ± 11.9 yrs). We used reverse phase-HPLC/FD for analysis of urinary BPA and obtained information from each subject on lifestyle, environment, and potential exposure to BPA via food. The HPLC/FD method showed good reproducibility (CVs < 0.1) and a relatively sensitive detection limit of 0.012 μg/L. These methods yielded a geometric mean of urinary BPA as 9.54 μg/L (8.91 μg/g creatinine), with a geometric standard deviation of 8.32 μg/L. Among potential routes for BPA exposure, only "vinyl wrapping of microwave heating" indicated a borderline positive association with urinary BPA level ($p = 0.1$). After PCR-RFLP, we found the allele frequencies of *SULT1A1*1* and *SULT1A1*2* were 0.89 and 0.11, respectively within the subjects. As the *SULT1A1*1* allele of SULT1A1 is known to be a rapid sulfonylation-allele, the presence of *SULT1A1*1* is suspected to rapidly dispose of environmental BPA. However resultant, urinary BPA levels were not significantly different between the *SULT1A1*1/*1* identified subjects and the *SULT1A1*1/*2* subjects. Therefore, to clarify host variability in urinary BPA level, different genetic polymorphisms in BPA metabolic enzymes other than SULT1A1 should be further studied.

Bisphenol A (2,2-bis(4-hydroxyphenyl)propane, BPA) is suspected to be an endocrine disruptor of the kind reported for such compounds as dioxin and polychlorinated biphenyls (Roy *et al.* 1997; The Bisphenol A Global Industry Group 2002; Safe 2000). BPA-derived polycarbonate and epoxy resins have been used for drinking water containers, baby bottles, dental sealing, and coating food cans (Roy *et al.* 1997; BAGIG). BPA itself has been widely used in plastic manufacture and as an antioxidant in brake fluid, rubber, and soaps, as a preservative for cable covering and textiles, as a dye enhancer in polyesters and polyolefins, and as a stabilizer in polyvinyl chloride plastic (BAGIG). Thus, people can be easily and continuously exposed to BPA in their daily environment (Howe *et al.* 1999; Biles *et al.* 1999; Mountfort *et al.* 1999; Lee *et al.* 1999). Recently, the Korean FDA issued a warning regarding the migration of BPA from food-containers to foodstuffs by heating and high pressure methods (Lee *et al.* 1999). However, very few epidemiological studies have dealt with degree to which people are exposed to BPA. Therefore, biological monitoring of BPA exposure is needed for BPA risk assessment.

In order to conduct proper biological monitoring of xenobiotics, the individual differences in the metabolism of xenobiotics, i.e. susceptibility biomarkers, should be determined and considered. BPA is metabolized by phase I and II enzymes and excreted in stool and urine (Nakagawa *et al.* 2000). Hence, variation in BPA-metabolic enzymes may bring out alteration in BPA inactivation/disposal paradigms. Among phase II enzymes, sulfotransferases (SULTs) and uridine diphosphate glucuronosyltransferases (UGTs) are known to be involved in BPA metabolism (Elsby *et al.* 2001; Yokota *et al.* 1999; Suiko *et al.* 2000; Raftogianis *et al.* 1997). Among SULTs, SULT1A1 is thought to sulfate phenolic compounds like BPA, and is considered to be genetically polymorphic (Raftogianis *et al.* 1997; Nowell *et al.* 2000; Carlini *et al.* 2001) in human. There are four known different alleles in *SULT1A1*, and are reported as: *SULT1A1*1*, *SULT1A1*2*, *SULT1A1*3*, and *SULT1A1*4* in the literature. Furthermore, there are suspected ethnical differences in the frequencies of these alleles. Although *SULT1A1*1* and *SULT1A1*2* are common in Caucasian populations, the frequency of the latter is rare in the Chinese populations (Carlini *et al.* 2001). The *SULT1A1*2* allele has an A to G transition at nucleotide 638 in exon 7 of *SULT1A1*. This

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transition results in an Arg 213 to His alteration in the amino acid sequence and leads to lower enzyme activity in people with *SULT1A1*2* than in people with *SULT1A1*1* (Raftogianis *et al.* 1997; Nowell *et al.* 2000; Carlini *et al.* 2001). Thus, urinary BPA levels can be affected by the genetic polymorphism of *SULT1A1*.

In this study, we conducted biological monitoring of environmental BPA using urinary BPA as the exposure biomarker for BPA in a Korean population. Moreover, we investigated the effects of *SULT1A1* genetic polymorphism on urinary BPA levels and investigated possible BPA exposure routes via food.

Methods and Materials

Subjects

Study subjects were 73 Koreans who were not occupationally exposed to BPA, were not taking medicine, and who lived within Daejon, an urban city in central South Korea. Thirty-four males and 39 females, with the mean age of 48.5 ± 11.9 years, with mean weight of 64.1 ± 10.8 kg, and mean height of 162.5 ± 9.5 cm, served as subjects. All subjects gave informed consents. Peripheral blood and morning spot urine specimens were collected from each subject before breakfast. The subjects were required to fill out questionnaires, which reflected occupation, education, and lifestyle habits, such as tobacco smoking, alcohol consumption, and other common demographic qualities from which we could extrapolate potential exposure to BPA via such food sources as the consumption of canned goods, bottled beer, instant noodles, and the use of products with microwave wrapping or other polyvinyl packaging that comprise the plastics found in food storage containers.

Analysis of Urinary BPA

We modified the method used by Matsumoto *et al.* (2001) to measure conjugated forms of urinary BPA. The free form of BPA was also analyzed to exclude contamination of BPA in sampling or experimental process (Figure 1).

Briefly, for the analysis of total urinary BPA (conjugated or free form), 30 μl of 2.0 M sodium acetate (pH 5.0), and 10 μl of β-glucuronidase (Sigma, St. Louis MO) were added to 500 μl aliquots of each urine sample present in a 15-ml glass tube. The reaction mixture was incubated at 37°C for 3 h. To analyze the free form of BPA, the above method was duplicated without the addition of β-glucuronidase. After the incubation, we added 100 μl of 2 N HCl and extracted the mixture with 5 ml of ethylacetate that included 100 ng/ml bisphenol B (Tokyo Kasei Kogyo, Tokyo, Japan) as an international standard. After the extraction, we transferred 2 ml of supernatant to a new glass tube and evaporated the solution. The residue was dissolved in 200 μl of 60% acetonitrile and 120 μl of this resultant was injected into our HPLC/FD apparatus (Waters 515 HPLC Pump with automated gradient controller, Waters 717 plus auto sampler, and the 474 Scanning Fluorescence Detector). HPLC parameters were as follows: Waters X Terra RP18, 5 m (4.6 mm × 250 mm) column; mobile phase A, 2.5% tetrahydrofuran in water; mobile phase B, acetonitrile; 0–30 min, flow rate was 1.0 ml/min, ratio of A to B ranged from 70:30 to 40:60; 30–35 min, 1.0 ml/min, 40:60 to 0:100; 35–40 min, 1.0 ml/min, 0:100; 40–45 min, 0:100 to 70:30; 45–60 min, 1.0 ml/min, 70:30; fluorescence, excitation 275 nm, emission 300 nm. The concentration of conjugated BPA was calculated after subtracting the amount of the free form of BPA from that of total BPA. In addition, the BPA concentration was adjusted for urinary creatinine concentration to correct urine volume. Urinary creatinine was analyzed by the method described by Ogata and Taguchi (1988).

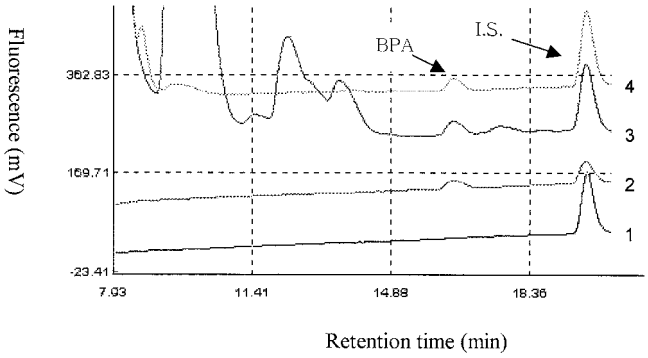

Figure 1. Chromatograms of blank (1), standard mixture (2), and an urine sample, total BPA (3), and free form of BPA (4). Retention time of BPA and internal standard (I.S., bisphenol B), 16.4 min and 19.7 min, respectively.

The BPA fraction, which was obtained from the above HPLC/FD, was confirmed by LC/MS/ESI/SIM (Agilent, 1100 Series LC/MSD; column, Zobax c-18 (3.5 μm × 7.5 cm); mobile phase, water to acetonitrile was 50:50, including 3% acetic acid; flow rate, 1 ml/min; MSD fragmentation, V = 100; monitored using the pseudomolecular ion $(M\text{-H})^-$ = 227 and $(M\text{-H-CH}_3)^-$ = 212 of BPA (Figure 2).

Determination of SULT1A1 Genotype

Genomic DNA was isolated from peripheral blood using a Wizard Genomic DNA purification kit (Promega, Madison, WI) according to the manufacturer's instructions. PCR amplifications and RFLP analyses were performed as described by Coughtrie *et al.* (1999) with minor modification. Forward and reverse primers were 5′-gttggctctg-cagggtctctagga-3′ and 5′-cccaaacccccgtactggccagcaccc-3′, respectively. In brief, 1 μl (approximately 200 ng) of genomic DNA and 20 pmol of each primer were added to a universal PCR mixture (Bioneer, Daejon, Korea). Twenty μl of the PCR reaction mixture were applied for PCR. After *HaeII* digestion, we determined genotypes of *SULT1A1*.

Statistical Analysis

The statistical analyses for the categorized variables comprising environmental BPA exposure were defined as follows: consumption of canned fish or ham, ≥ 3 cans/week = 3, 1–2 cans/week = 2, 1–3 cans/month = 1, never consumed = 0; consumption of bottled beer, ≥10 bottles/week = 4, 5–9 bottles/week = 3, 1–4 bottles/week = 2, 1–3 bottle/month = 1, never consumed = 0; consumption of instant noodle, ≥3 packs/week = 3, 1–2 packs/week = 2, 1–3 packs/month = 1, never consumed = 0; wrapping food for microwave heating, always (100%) = 3, frequently (50%≤ and <100%) = 2, occasionally (0< and <50%) = 1, never (0%) = 0; frequency of microwave use, several times/day = 3, several times/week = 2, several times/month = 1, never = 0. Spearman Rank Correlation was used to study the relationships between urinary BPA levels and expected routes for BPA exposure: Partial correlation was performed to adjust for age and sex. Mann-Whitney U test was used to study the associations between urinary BPA levels and the *SULT1A1* genotypes. The *p*-values for all

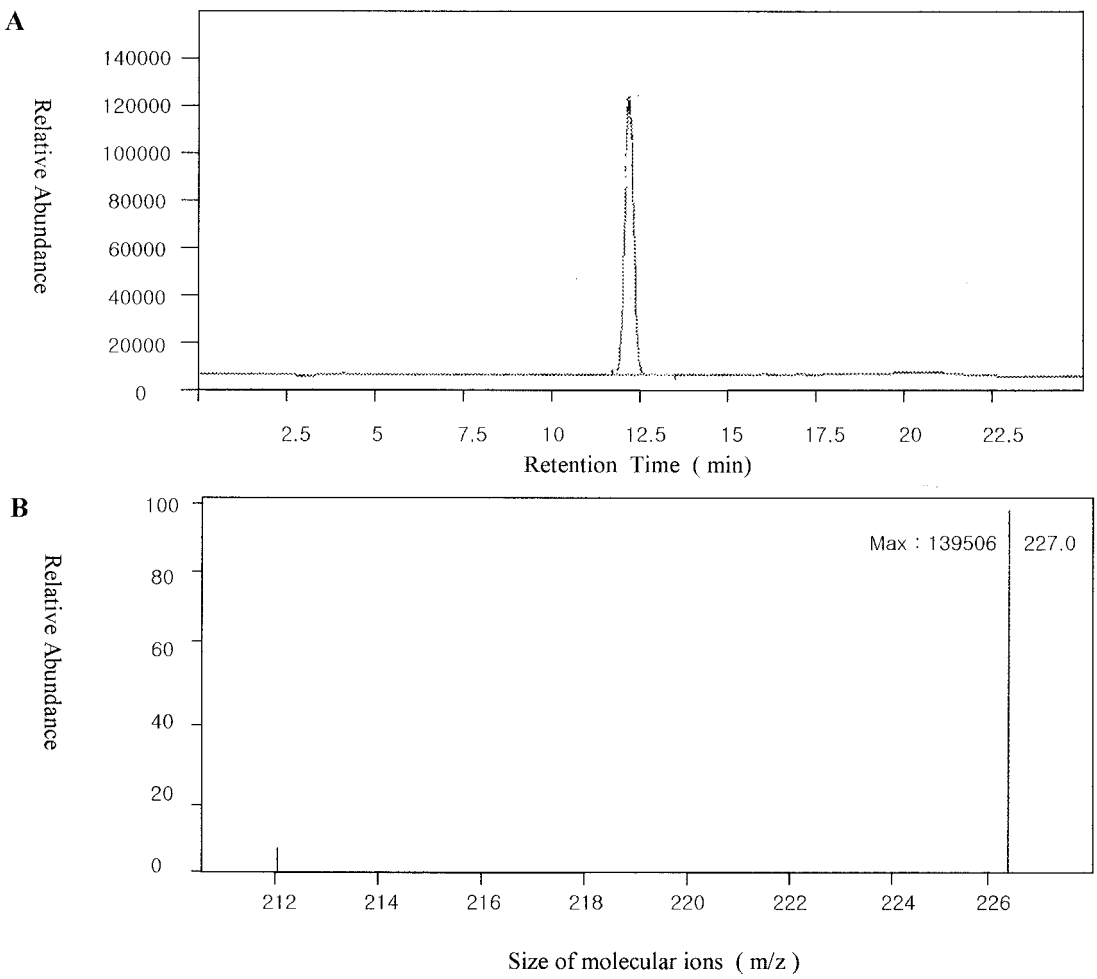

Figure 2. Identification of BPA: LC/MS/SIM profile (**A**) and MS profile (**B**) of the BPA fraction, which was obtained from HPLC/FD

tests were computed with JMP® (SAS Institute, Inc., Cary, NC) and used for significance evaluation.

Results

Characteristics of Subjects

Table 1 shows the characteristics of the subjects. In term of educational and occupational level, the subjects were somewhat below the middle class in Korea (Koreans' mean period of education was 10.5 years in 1995; Korean National Statistical Office 2000). The ratio of smokers in the subjects was almost the same as those of ordinary Koreans in 1998, 36.2% (Korean National Statistical Office 2000). The data of *SULT1A1* genotypes as presented in the table is the first report concerning the distribution of *SULT1A1* genetic polymorphisms in the Korean population. Allele frequencies in this Korean population, 0.89 and 0.11 for *SULT1A1*1* and *SULT1A1*2*, respectively, followed the Hardy-Weinberg law. These frequencies are quite different from those of the Caucasians (0.70 and 0.30, respectively; Carlini *et al.* 2001), but are similar to those of the Chinese population (0.91 and 0.08, respectively; Carlini *et al.* 2001). The Korean subjects used plastic containers as their main food containers, rather than glass or vinyl pack/wrap.

Distribution of Urinary BPA

The detection limit of BPA with the HLPC method was 0.012 μg/L. Table 2 presents the reproducibility of BPA analysis by the HPLC method (n = 5). Since we obtained acceptable coefficient of variations (CVs) in our results, we analyzed for BPA in all urine samples with the HPLC method and were able to measure urinary BPA in 75% of the subjects. We confirmed the BPA fraction of the HPLC method with the LC/MS.

BPA was not detected in blank tests, which were conducted with water instead of urine. Thus, we confirmed an absence of BPA contamination in the whole of our experimental process (Figure 1). Following exclusion of BPA non-detectable samples, the range of urinary BPA levels was 0.68–586.14 μg/L. For statistical analysis, non-detectable

Table 1. Characteristics of subjects

Item	No. of items
Education[a] (yrs)	9.6 ± 4.1
Tobacco-smoking status (%)	
Smokers	37
Non-smokers	63
Frequency of alcohol drinking (%)	
>4 times/month	23
2–4 times/month	17
Non-drinkers (<2 times/month)	60
SULT1A1 genotype (%)	
*SULT1A1*1/*1*	78
*SULT1A1*1/*2*	21
*SULT1A1*2/*2*	1
Main container for food storage (%)	
Plastic	56
Glass	34
Vinyl pack or wrap	10

[a] Since elementary school.

was assigned a value of half of the minimum value of detected urinary BPA, i.e. 0.34 μg/L. As the distribution of BPA level was not normal distribution, we logarithmically transformed the BPA level: geometric mean (GM), 9.54 μg/L (8.91 μg/g creatinine); geometric standard deviation (GSD), 8.32.

BPA Exposure Routes

To find the exposure routes of environmental BPA, particularly via food, we studied the association between urinary BPA and the potential BPA exposure routes (Table 3). As results, there were somewhat positive associations between urinary BPA and the consumption of canned beverage, fish, and ham, and frequent use of vinyl in the microwave. After adjusting for age and sex, there was a borderline significance between urinary BPA level and the frequency with which vinyl wrapping was used in the microwave" ($p = 0.10$). However, none of the other BPA potential routes were significantly associated with urinary BPA level.

Effects of Genetic Polymorphism in SULT1A1 on Urinary BPA Levels

Since the *SULT1A1*1* allele is known to be a rapid sulfonylation-allele, the presence of *SULT1A1*1* is suspected to contribute to the rapid excretion of environmental BPA. Indeed the GM of urinary BPA level was somewhat higher in the *SULT1A1*1/*1* subjects than that found in the *SULT1A1*1/*2* subjects, although not to a significant degree (Table 4). When the subjects were separated according to their use of vinyl wrapping in the microwave, we also did not find any significant differences in urinary BPA levels by genetic polymorphism of SULT1A1, i.e. after adjusting for BPA exposure level, SULT1A1 genetic polymorphism did not affect urinary BPA level. Due to the inclusion of only one *SULT1A1*2/*2* subject, we did not investigate differences in urinary BPA levels between the *SULT1A1*2/*2* subjects and either the *SULT1A1*1/*1* or *SULT1A1*1/*2* subjects.

Table 2. Reproducibility of BPA analysis by HPLC

BPA concentration (μg/L)	Mean area of HPLC	Standard Deviation	CV
0.4	21.5	0.7	0.03
1.2	82.3	5.5	0.06
3.7	281.0	18.2	0.06
11.1	898.0	45.5	0.05
33.3	2840.0	199.0	0.07
100.0	8463.0	521.0	0.06

Discussion

In this study, the HPLC/FD method showed good reproducibility for BPA analysis (Table 2). It also features benefits including low cost, convenience via ease of preparation and handling of samples, availability, etc. We were able to analyze 75% of all subjects by the HPLC/FD method and maintain a relatively sensitive detection limit, 0.012 μg/L, compared to other methods such as HPLC/ED (detection limit, 0.01 μg/L; Inoue *et al.* 2000). We therefore recommend the HPLC/FD method for the analysis of urinary BPA. However, for more rigid regulation of BPA exposure, the exposure level of BPA will be further reduced, requiring the development of more sensitive and convenient methods for the future analysis of urinary BPA.

The urinary BPA levels in our Korean subjects were approximate 9.5 μg/L. Since there are very few papers concerning urinary BPA levels in normal populations, our result will provide useful data for the extrapolation of risk assessment of BPA exposure via these routes reported herein. For example, the occurred urinary BPA level can be used to estimate the daily BPA exposure level using physiologically based pharmacokinetic (PBPK) model (Jang *et al.* 2001).

In the present study, we could not find any significant association between urinary BPA levels and BPA exposure routes via food containers (Table 3). This lack of association may have resulted from the absence of primary BPA exposure sources or from the low ratio of BPA exposure level via food to total BPA exposure. Non-BPA chemicals such as polyethylene were recently substituted for can coating and vinyl wrap in Korea. This kind of endeavor is thought to have contributed to lowering the level of BPA exposure. Besides being a component of polycarbonate plastics, BPA is also used as an additive in PVC (Roy *et al.* 1997; BAGIG). In other words, the use of PVC, rather than plastic containers or beverage cans, is suspected as a main exposure route for environmental BPA. Thus, in the present study, we investigated whether PVC-capped beer or PVC-packed instant noodles were routes of BPA exposure. However, they were not found to be associated with urinary BPA levels (Table 3). Thus, various other routes of environmental exposure to BPA should be explored.

In an effort to conduct proper biological monitoring of BPA exposure, susceptibility biomarkers should be discovered and considered. Towards this end, we considered the effects of

Table 3. Association between urinary BPA level and its potential exposure routes

BPA exposure routes	Correlation coefficient[a]	*p* value	Adjusted *p* value[b]
Canned beverage[c]	0.17	0.19	0.32
Canned fish/ham	0.08	0.54	0.28
Bottle beer	−0.09	0.46	0.59
Instant noodle	−0.05	0.70	0.55
Vinyl wrapping for microwave[d]	0.12	0.33	0.10
Vinyl pack for food storage[e]	−0.11	0.39	0.36
Plastic container for food storage[f]	−0.07	0.58	0.56

[a] Spearman's Rho.
[b] Adjusted for age and sex.
[c] Number of canned beverage/week.
[d] Wrapping food for microwave heating × frequency of microwave heating.
[e,f] % of vinyl pack and plastic containers, respectively, in each subject's food containers.

Table 4. Differences in urinary BPA level by the *SULT1A1* genetic polymorphism

		Urinary BPA level			
*SULT1A1*1* genotype	No. of subjects (%)	GM (μg/L)	GSD	*p* value[a]	Adjusted *p* value[b]
All subjects					
*SULT1A1*1/*1*	57 (78.08)	10.10	8.71	0.58	0.39
*SULT1A1*1/*2*	15 (20.54)	6.31	8.91		
*SULT1A1*2/*2*	1 (1.37)	60.20	—		
Column total	73 (100)	9.54	8.32		
Low use of vinyl wrapping in the microwave					
*SULT1A1*1/*1*	35 (81.39)	9.12	9.55	0.68	0.57
*SULT1A1*1/*2*	7 (16.28)	5.49	10.00		
*SULT1A1*2/*2*	1 (2.33)	60.20	—		
Column total	43 (100)	7.24	9.05		
High use of vinyl wrapping in the microwave					
*SULT1A1*1/*1*	22 (73.33)	11.75	7.59	0.71	0.31
*SULT1A1*1/*2*	8 (26.67)	7.24	9.33		
*SULT1A1*2/*2*	—	—	—		
Column total	30 (100)	14.13	7.24		

[a] Differences between the *SULT1A1*1/*1* and *SULT1A1*1/*2* present subjects.
[b] Adjusted for age and sex.

genetic polymorphisms at *SULT1A1* on urinary BPA levels. Conjugation of BPA may decrease BPA estrogen activity and prevent BPA biotransformation to bisphenol quinones that adduct DNA (Atkinson *et al.* 1995). Therefore, people with the rapid sulfonylation alleles would be less susceptible to BPA toxicity and would have higher levels of conjugated BPA in urine. As the *SULT1A1*1* allele is known to be rapid sulfonylation allele (Raftogianis *et al.* 1997; Nowell *et al.* 2000), its presence is suspected to assist rapid disposal of environmental BPA sources. However, urinary BPA levels were not significantly different between *SULT1A1*1/*1* subjects and *SULT1A1*1/*2* subjects in our study (Table 4). After adjusting for BPA exposure level, such as the route suspected via the use of vinyl wrapping in the microwave, the genetic polymorphism of SULT1A1 also did not affect urinary BPA levels (Table 4). Raftogianis *et al.* (1997) found significantly lower SULT1A1 activity in *SULT1A1*2/*2* subjects than in the *SULT1A1*1/*1* subjects and *SULT1A1*1/*2* subjects, but they did not find any additional activity differences between the *SULT1A1*1/*1* subjects and the *SULT1A1*1/*2* subjects. Consequently, with no SULT1A1 activity differences between the *SULT1A1*1* homozygous subjects and the heterozygous subjects of the *SULT1A1*1* and *SULT1A1*2*, resultant urinary BPA levels between these two groups may be unchanged. On the other hand, the presence of only one *SULT1A1*2/*2* subject in our subjects means that the low frequency of the *SULT1A1*2* allele (Table 1) may have prevented the genetic polymorphism of *SULT1A1* from affecting the urinary BPA levels in our Korean population (Table 4). By contrast, we used β-glucuronidase/sulfatase for urine hydrolysis, it is believed hydrolyzed urinary BPA comes from glucuronyl and sulfonyl conjugated BPA. Elsby *et al.* (2001) reported that the amounts of BPA sulfates were less than those obtained from BPA glucuronide in rat hepatocytes—even human liver microsomes did not glucuronidate BPA as extensively as the rat liver microsomes. Thus, excretion of BPA by glucuronidation can also mask the effects of variations in SULT activity on urinary BPA. Genetic polymorphisms, not only in SULT1A1 but also in UGTs (Mackenzie *et al.* 2000), should be discovered and studied to clarify host variability in urinary BPA level in the near future.

In conclusion, we determined that urinary BPA levels were approximately 9.5 μg/L in the Korean population. Among the potential routes of environmental BPA exposure, the use of vinyl wrapping in the microwave is suspected as the imminent

exposure route for BPA in our study population. Allele frequencies of *SULT1A1*1* and *SULT1A1*2* within our study group were 0.89 and 0.11, respectively. Urinary BPA levels were not significantly different between the *SULT1A1*1/*1* and *SULT1A1*1/*2* subjects. Therefore, to clarify host variability in urinary BPA levels, different genetic polymorphisms in BPA metabolic enzymes other than SULT1A1 should be further studied.

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