Environmental Science & Technology

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pubs.acs.org/est

Bisphenol S in Urine from the United States and Seven Asian Countries: Occurrence and Human Exposures

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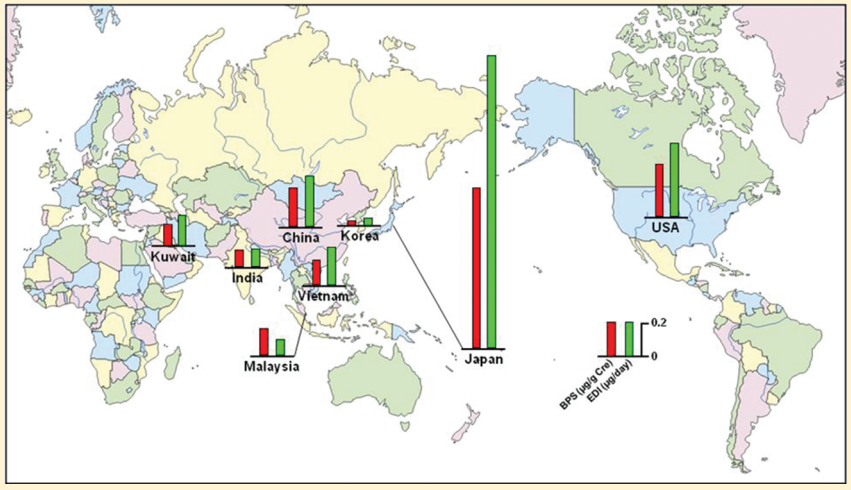
Supporting Information



ABSTRACT: As concern regarding the toxic effects of bisphenol A (BPA) grows, BPA in many consumer products is gradually being replaced with compounds such as bisphenol S (BPS). Nevertheless, data on the occurrence of BPS in human specimens are limited. In this study, 315 urine samples, collected from the general populations in the United States, China, India, Japan, Korea, Kuwait, Malaysia, and Vietnam, were analyzed for the presence of total BPS (free plus conjugated) concentrations by high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS). BPS was detected in 81% of the urine samples analyzed at concentrations ranging from below the limit of quantitation (LOQ; 0.02 ng/mL) to 21 ng/mL (geometric mean: 0.168 ng/mL). The urinary BPS concentration varied among countries, and the highest geometric mean concentration [1.18 ng/mL or 0.933 μg/g creatinine (Cre)] of BPS was found in urine samples from Japan, followed by the United States (0.299 ng/mL, 0.304 μg/g Cre), China (0.226 ng/mL, 0.223 μg/g Cre), Kuwait (0.172 ng/mL, 0.126 μg/g Cre), and Vietnam (0.160 ng/mL, 0.148 μg/g Cre). Median concentrations of BPS in urine samples from the Asian countries were 1 order of magnitude lower than the median concentrations reported earlier for BPA in the same set of samples, with the exception of samples from Japan.

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Received: April 4, 2012
Revised: May 22, 2012
Accepted: May 23, 2012
Published: May 23, 2012

There were no significant differences in BPS concentrations between genders (male versus female), or among age groups (categorized as ≤19, 20−29, 30−39, 40−49, and ≥50 years), or races (Caucasian versus Asian). The daily intake (EDI) of BPS was estimated on the basis of urinary concentrations using a simple pharmacokinetic approach. The median EDI values of BPS in Japan, China, United States, Kuwait, Vietnam, Malaysia, India, and Korea were 1.67, 0.339, 0.316, 0.292, 0.217, 0.122, 0.084, and 0.023 μg/person, respectively. This is the first study to report the occurrence of BPS in human urine.

INTRODUCTION

Bisphenol analogues are widely used in industrial and consumer products. Among these compounds, bisphenol A (BPA), produced in quantities of over eight billion pounds each year worldwide, is frequently used in the production of polycarbonate plastics and of the resin lining of food and beverage cans.[1,2] Widespread occurrence of BPA in environmental matrices, including air, water, sewage sludge, soil, house dust, and foodstuffs[3−9] as well as human urine, blood, breast milk, and saliva is known.[10−14] BPA also has been shown to occur in various paper products and paper currencies.[15,16] BPA exposures have been associated with a wide array of adverse health outcomes,[17−19] even at doses on the order of tens to hundreds of nanograms per kilogram body weight (bw).[20−22] Concerns about the health risks of BPA are increasing, and restrictions/regulations have been put forward to limit its application in some consumer products.[23,24]

BPA is being replaced with a number of alternatives, such as bisphenol S (BPS; 4,4′-sulfonyldiphenol), bisphenol B [BPB; 2,2′-bis(4-hydroxyphenyl)butane], bisphenol F (BPF; 4,4′-dihydroxydiphenylmethane), and bisphenol AF [BPAF; 4,4′-(hexafluoroisopropylidene)diphenol].[25−27] These bisphenol analogues also are used in the production of polycarbonate plastics and resins.[25,26] BPS and BPA have been found in canned foodstuffs at concentrations on the order of several tens of nanograms per gram.[28,29] BPF has been reported to occur in surface water, sewage, and sediments at concentrations ranging from 0.0001 to 0.180 μg/L, 0.022 to 0.123 μg/L, and 1.2 to 7.3 μg/kg, respectively.[30] BPB has been found in human serum from Italy at concentrations ranging from 0.88 to 11.9 ng/mL.[27]

Limited studies have shown that BPS, BPB, and BPF possess acute toxicity, genotoxicity, and estrogenic activity, similar to BPA.[25,26,31−34] BPB and BPAF were reported as agonists of the human pregnane X receptor, a nuclear receptor that functions as a regulator of xenobiotic metabolism.[35] The environmental biodegradation rates of BPS and BPB were similar to or less than those of BPA.[36] Although considerable controversy still surrounds the safety of BPA,[18] the potential for human exposure to alternatives to BPA cannot be ignored.

In the present study, total urinary BPS concentrations (free plus conjugated) were measured in 315 urine samples collected from the general populations in the United States and seven Asian countries: China, India, Japan, Korea, Kuwait, Malaysia, and Vietnam. The baseline urinary concentrations of BPS were established, and geographic patterns and profiles were determined. On the basis of the measured urinary concentrations, potential human exposure doses to BPS were estimated. This is the first study on the occurrence of BPS in human urine.

MATERIALS AND METHODS

Chemicals. BPS (purity: 98%), creatinine (99%), formic acid (98.2%), acetic acid (99.9%), and β-glucuronidase from *Helix pomatia* (145 700 units/mL β-glucuronidase; 887 units/mL sulfatase) were purchased from Sigma-Aldrich (St. Louis, MO). Ammonium acetate (98%), hydrochloric acid (HCl, 37%), and organic solvents (analytical grade) were purchased from Mallinckrodt Baker (Phillipsburg, NJ). Labeled $^{13}C_{12}$−BPA (99%) and creatinine-d_3 (99%) were purchased from Cambridge Isotope Laboratories (Andover, MA) and CDN Isotopes (Pointe-Claire, Quebec, Canada), respectively. Milli-Q water was provided through an ultrapure water system (Barnstead International, Dubuque, IA). The stock solutions of BPS and $^{13}C_{12}$−BPA were prepared at 1 mg/mL in methanol. The stock solutions of creatinine and creatinine-d_3 were prepared at 1 mg/mL in milli-Q water. All stock solutions were stored at −20 °C. The working solutions were prepared from the stock solutions through serial dilution with methanol or water.

Sample Collection. Urine samples (n = 315) were collected from the U.S. and seven Asian countries in 2010 and 2011. The urine samples (n = 31) from the U.S. were collected from Albany, New York. The urine samples from Asian countries were collected from the cities of Harbin and Shanghai (China; n = 89), Mettupalayam and Chennai (India; n = 38), Matsuyama and Kumamoto (Japan; n = 36), Seoul, Busan, and Yeosu (Korea; n = 33), Al-Asma and Al-Jahra governorates (Kuwait; n = 30), Kuala Lumpur (Malaysia; n = 29), and Hanoi (Vietnam; n = 29). Samples were collected from both males and females who ranged in age from 2 to 84 years (Table S1; Supporting Information). All samples were kept at −20 °C until analysis. The New York State Department of Health Institutional Review Board approved the study protocol for the analysis of urine.

Sample Preparation. Samples were extracted and analyzed for BPS by following the methods described elsewhere, with some modifications.[11,37] Briefly, after thawing at room temperature, 0.5 mL of urine was transferred into a 15-mL glass tube, and 50 μL of 100 ng/mL (5 ng) internal standard ($^{13}C_{12}$−BPA) and 1 mL of 1 M ammonium acetate buffer (pH 5.0; 7.71 g of ammonium acetate, dissolved in 93.8 mL of milli-Q water and 6 mL of acetic acid with 200 μL of β-glucuronidase) were added. The mixture was incubated at 37 °C for 12 h. After digestion, 0.24 mL of 1 M formic acid (pH 1.0; 3.93 mL of formic acid dissolved in 96.07 mL of water) and 1.21 mL of water were added (total volume: 3 mL). The extraction and purification of the sample were conducted with a RapidTrace SPE workstation (Caliper Life Sciences, Inc., Hopkinton, MA). The sample was loaded onto an Oasis MCX cartridge (60 mg/3 mL; Waters, Milford, MA), preconditioned with 5 mL of methanol and 5 mL of water. The cartridge was then washed with 2 mL of 0.1 N HCl and 5 mL of 40% methanol in water and eluted with 5 mL of methanol at 0.5 mL/min. The eluate was concentrated to 0.5 mL under a gentle stream of nitrogen and subjected to high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) analysis.

Instrumental Analysis. An Applied Biosystems API 5500 electrospray triple quadrupole mass spectrometer (ESI-MS/MS; Applied Biosystems, Foster City, CA), coupled with an Agilent 1100 Series HPLC system (Agilent Technologies Inc., Santa Clara, CA) was used for identification and quantification of BPS. Chromatographic separation was carried out by a Betasil C18 column (100 × 2.1 mm, 5 μm; Thermo Electron Corporation,

Waltham, MA), connected in series with a Javelin guard column (Betasil C18, 20 × 2.1 mm, 5 μm; Thermo Electron Corporation). The mobile phase used methanol and milli-Q water, and the gradient was as follows: 0−2 min, 15% methanol; 2−9 min, 15−90% methanol; 9−12 min, 90−99% methanol; 12−15 min, 99% methanol; and 15−20 min, 15% methanol. The injection volume was 10 μL, and the mobile phase flow rate was 300 μL/min. The negative ion multiple reaction monitoring (MRM) mode was used, and the MRM transitions monitored were 249 > 108 for BPS and 239 > 224 for $^{13}C_{12}$−BPA. Nitrogen was used as both a curtain and a collision gas. Cone voltage was −30 V, and collision energy was 22 V. Capillary voltage was kept at −4.5 kV, and desolvation temperature was 700 °C. The representative total ion chromatograms of a standard mixture and a urine sample, showing chromatographic resolution of the target compounds analyzed by HPLC-MS/MS, are shown in Figure S1 (Supporting Information).

Analysis of Creatinine. Ten microliters of urine was diluted with milli-Q water (160-fold), and 800 ng of creatinine-d_3 was added as an internal standard. Creatinine was analyzed with HPLC-MS/MS in an electrospray positive ionization mode, and the MRM transitions monitored were 114 > 44 for creatinine, and 117 > 47 for creatinine-d_3.[38] The separation was carried out isocratically, using 50% methanol in milli-Q water that contained 0.1% formic acid, at a flow rate of 300 μL/min for 5 min.

Quality Assurance and Quality Control (QA/QC). Because BPS can be present in many plastic products, glass containers were used in the analytical procedure. A procedural blank, a spiked blank, and two matrix-spiked samples were analyzed for each set of 20 samples, following the same procedure as described above. Procedural blanks were prepared by substitution of 0.5 mL of milli-Q water for urine, followed by passage through the entire analytical procedure. BPS was detected in procedural blanks at trace concentrations (approximately 0.0067 ng/mL). Background subtraction was performed in the quantification of BPS concentrations in samples. Ten nanograms of BPS were spiked into procedural blanks and sample matrixes, and the recoveries were 94 ± 13% and 92 ± 19% (mean ± SD), respectively. The limit of quantitation (LOQ) of BPS was 0.02 ng/mL, which was three times the average concentration found in procedural blanks. Quantification was performed by the isotope-dilution method. A midpoint calibration standard was injected to check for instrumental drift in sensitivity after every 20 samples, and a pure solvent (methanol) was injected to check for carry-over of BPS from sample to sample. Calibration standards (n = 10), prepared in methanol at concentrations ranging from 0.01 to 20 ng/mL, were injected daily, and the regression coefficient (r) was >0.99.

Daily Intake Calculation. Urinary BPA concentration has been used in the estimation of a human exposure dose.[39,40] Given the similarity in molecular structure between BPS and BPA, we estimated human exposure to BPS based on a model reported for BPA.[11,40]

Estimated daily intake (EDI; μg/day) = urinary BPS concentration (μg/L) × urine excretion rate (L/day). The urine output varies by age and sex and is reported to be about 1.2−2 L/day for adults.[40,41] Values for daily urine excretion rate used in our exposure assessment were adopted from the reference values given by the International Commission on Radiological Protection (ICRP).[41] According to the ICRP, gender difference in urine excretion rate is observed for adults (≥20 years), and the rates are 1.6 and 1.2 L/day for men and women, respectively. The reported ICRP urine excretion rates for 5-, 10-, and 15-year old individuals were 0.5, 0.7, and 1.2 L/day, respectively, for both male and female subjects, which were used for individuals of ages 2 to ≤5 years, 6−10 years, and 11−19 years, in our calculations.

Statistical Analysis. Data analysis was performed with Origin 7.5 or SPSS 17.0. Concentrations below the LOQ were substituted with a value equal to LOQ divided by 2 or the square root of 2 for the calculation of the arithmetic mean and geometric mean (GM), respectively. Differences between groups were compared by a one-way ANOVA and the Tukey test. Values of $p < 0.05$ denoted significance.

RESULTS AND DISCUSSION

Urinary BPS Concentrations. BPS was found in 81% of the urine samples analyzed, at concentrations ranging from below the LOQ (i.e., 0.02 ng/mL) to 21.0 ng/mL, with a mean value of 0.654 ng/mL (Table 1). The GM and median concentrations of BPS were 0.168 and 0.191 ng/mL, respectively. The creatinine-adjusted mean, GM, and median concentrations of BPS were 0.598, 0.176, and 0.200 μg/g Cre, respectively (Table 1). The highest GM concentration (1.18 ng/mL, 0.933 μg/g Cre) of BPS was found in urine samples from Japan, followed (in decreasing order) by the U.S. (0.299 ng/mL, 0.304 μg/g Cre), China (0.226 ng/mL, 0.223 μg/g Cre), Kuwait (0.172 ng/mL, 0.126 μg/g Cre), and Vietnam (0.160 ng/mL, 0.148 μg/g Cre). The GM concentrations of BPS in urine samples from Japan were an order of magnitude higher than the concentrations measured in samples from India (0.072 ng/mL, 0.098 μg/g Cre) and Korea (0.030 ng/mL, 0.031 μg/g Cre) (one-way ANOVA, $p < 0.05$). BPS was found in 100% of the samples from Japan and Vietnam, followed (in decreasing order) by the U.S. (97%), China (82%), India (76%), and Malaysia (76%) (Table 1). Relatively higher concentrations and detection frequencies of BPS in urine samples from Japan and the U.S. were in accordance with the efforts to replace BPA with BPS in recent years. Japan has phased out BPA in thermal receipt papers since 2001 and made an effort to develop alternatives, including BPS.[42] A major manufacturer of thermal receipt papers in the U.S. announced replacement of BPA with BPS in 2006.[43,44]

Urine has been used for biomonitoring to assess human exposures to environmental contaminants.[10,11,39−41] Due to the variability in the volume of spot urine samples (that can influence concentrations of contaminants), adjustment of urinary data to creatinine content is performed to correct for variable volumes.[45] That is, the concentration of a contaminant in urine (volume-based concentration, usually expressed as nanogram per microliter) is divided by the creatinine concentration (microgram per microliter), to provide creatinine-adjusted concentration (microgram chemical per gram creatinine). Pearson correlation analysis showed that there existed a significant positive correlation between unadjusted and creatinine-adjusted BPS concentrations in urine samples, regardless of individual countries or the entire sample set from eight countries, with the exception of samples from Malaysia ($p < 0.01$; Table S2, Supporting Information). A positive correlation also was found between BPS and creatinine concentrations in urine samples (the entire sample set, $r = 0.230$, $p < 0.01$). These findings suggest that the urine excretion volume at sampling did not influence the concentrations of BPS.

Most of the urine samples from Asian countries (n = 296) analyzed in the present study had previously been analyzed for BPA.[11] Overall, the GM concentrations of BPA in urine samples from each country were higher than those of BPS. For example,

Table 1. Concentrations of Urinary Bisphenol S (ng/mL; μg/g Cre) in Albany, New York, U.S., and Seven Asian Countries

variable	n^a	mean ± SD	GM[b]	fifth percentile	median	95th percentile	range	detection rate (%)
country								
USA	31	1.12 ± 3.74	0.299	0.079	0.263	2.65	<LOQ[c]−21.0	97
		0.576 ± 1.34[d]	***0.304***	***0.103***	***0.262***	***1.40***	***<LOQ−7.57***	
China	89	0.525 ± 0.620	0.226	0.014	0.297	1.73	<LOQ−3.16	82
		0.632 ± 0.979	***0.223***	***0.008***	***0.300***	***2.51***	***<LOQ−6.64***	
India	38	0.171 ± 0.239	0.072	0.014	0.055	0.713	<LOQ−0.881	76
		0.393 ± 0.978	***0.098***	***0.009***	***0.111***	***1.50***	***<LOQ−4.72***	
Japan	36	2.27 ± 2.57	1.18	0.212	1.04	7.76	0.147−9.57	100
		1.64 ± 2.43	***0.933***	***0.191***	***0.827***	***4.83***	***0.148−14.0***	
Korea	33	0.099 ± 0.340	0.030	0.014	0.014	0.174	<LOQ−1.98	42
		0.119 ± 0.465	***0.031***	***0.009***	***0.025***	***0.121***	***<LOQ−2.70***	
Kuwait	30	0.785 ± 2.18	0.172	0.014	0.371	1.65	<LOQ−12.1	70
		0.558 ± 1.26	***0.126***	***0.008***	***0.158***	***1.78***	***<LOQ−6.69***	
Malaysia	29	0.128 ± 0.170	0.071	0.014	0.084	0.252	<LOQ−0.922	76
		0.485 ± 1.08	***0.155***	***0.027***	***0.121***	***2.36***	***<LOQ−5.22***	
Vietnam	29	0.198 ± 0.164	0.160	0.048	0.157	0.385	0.037−0.932	100
		0.185 ± 0.140	***0.148***	***0.059***	***0.129***	***0.419***	***0.050−0.660***	
gender								
male	152	0.828 ± 1.75	0.239	0.014	0.226	3.81	<LOQ−12.1	86
		0.692 ± 1.47	***0.233***	***0.011***	***0.261***	***2.77***	***<LOQ−14.0***	
female	150	0.515 ± 1.81	0.126	0.014	0.160	1.60	<LOQ−21.0	75
		0.532 ± 1.11	***0.145***	***0.009***	***0.169***	***2.31***	***<LOQ−7.57***	
age								
≤19 yrs	33	0.460 ± 0.491	0.268	0.014	0.412	1.36	<LOQ−2.39	91
		0.798 ± 1.29	***0.305***	***0.015***	***0.302***	***2.69***	***<LOQ−6.64***	
20−29 yrs	90	0.826 ± 2.50	0.151	0.014	0.168	3.47	<LOQ−21.0	76
		0.619 ± 1.18	***0.172***	***0.008***	***0.206***	***2.42***	***<LOQ−7.57***	
30−39 yrs	62	0.979 ± 1.86	0.244	0.014	0.246	6.00	<LOQ−8.13	82
		0.861 ± 1.94	***0.243***	***0.009***	***0.239***	***2.87***	***<LOQ−14.0***	
40−49 yrs	52	0.400 ± 0.650	0.142	0.014	0.154	1.47	<LOQ−3.25	83
		0.297 ± 0.360	***0.142***	***0.012***	***0.199***	***0.930***	***<LOQ−1.78***	
≥50 yrs	61	0.521 ± 1.56	0.164	0.014	0.185	1.54	<LOQ−12.1	84
		0.554 ± 1.20	***0.169***	***0.012***	***0.172***	***3.55***	***<LOQ−6.69***	
all	315	0.654 ± 1.75	0.168	0.014	0.191	2.50	<LOQ−21.0	81
		0.598 ± 1.29	***0.176***	***0.009***	***0.200***	***2.62***	***<LOQ−14.0***	

[a] *n*: number of samples. [b] GM: geometric mean. [c] LOQ: 0.02 ng/mL. [d] Bold italic: creatinine-adjusted concentration (μg/g Cre).

creatinine-adjusted GM concentrations of BPA in urine from China, India, Korea, and Kuwait were 1.03, 2.51, 2.53, and 1.09 μg/g Cre, respectively (Figure 1; data cited from ref 11); the corresponding GM concentrations of BPS in these countries were 0.223, 0.098, 0.031, and 0.126 μg/g Cre, respectively (Figure 1). One exception was the samples from Japan, which contained a greater GM concentration (0.933 μg/g Cre) of BPS than that of BPA (0.67 μg/g Cre). When the data for all seven Asian countries were combined, the GM concentrations (1.20 ng/mL, 1.25 μg/g Cre) of BPA were 1 order of magnitude higher than those (0.158 ng/mL, 0.166 μg/g Cre) of BPS (samples from the U.S. were excluded). Pearson correlation analysis indicated a significant correlation between BPA and BPS concentrations in the urine samples ($r = 0.142$, $p < 0.05$), which suggests that the exposure sources for these two types of bisphenols might be similar. Our results highlight widespread occurrence of BPS in urine from the U.S. and seven Asian countries.

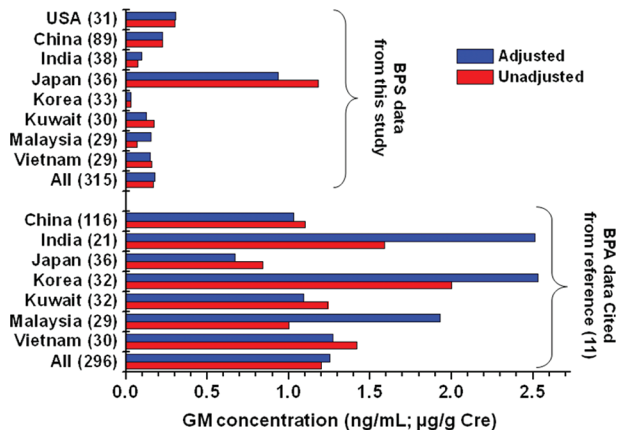

Figure 1. Geometric mean concentrations of BPS in human urine samples from the U.S. and Asian countries, in comparison with geometric mean concentrations of BPA. The numbers within parentheses on the *x*-axis represent the number of samples analyzed.

Gender, Age, and Ethnic Differences in BPS Concentrations. Gender-related differences in the concentrations of BPS between male and female subjects were examined for individual countries. The GM concentrations of urinary BPS in Vietnamese males ($n = 13$; 0.176 ng/mL and 0.196 μg/g Cre) were significantly higher than those ($n = 16$; 0.148 ng/mL and 0.118 μg/g Cre) in Vietnamese females ($p < 0.05$). However, no significant differences were found in urinary BPS concentrations

dx.doi.org/10.1021/es301334j | Environ. Sci. Technol. 2012, 46, 6860−6866

between males and females from other countries ($p > 0.05$). The overall difference in BPS concentrations between males and females (0.239 ng/mL and 0.233 μg/g Cre versus 0.126 ng/mL and 0.145 μg/g Cre; Table 1) also was not significant when the entire data set from all eight countries was collectively analyzed ($p > 0.05$). These results were similar to what was found previously for BPA in the same set of samples.[11]

We categorized the samples into five age groups, namely ≤19, 20−29, 30−39, 40−49, and ≥50 years, for the examination of the relationship between age and BPS concentrations. Among the five age groups, for the entire data set, the highest concentrations of BPS in urine samples were found in the age group of ≤19 years ($n = 33$), with GM and median concentrations of 0.305 and 0.302 μg/g Cre; followed by the group of 30−39 years ($n = 62$; 0.243 and 0.239 μg/g Cre), and 20−29 years ($n = 90$; 0.172 and 0.206 μg/g Cre) (Table 1). Relatively higher urinary BPA concentrations in teenagers and young adults than in adults has been reported previously,[10,11] and a similar trend was found for BPS. High concentrations of BPS in teenagers and young adults may be related to canned food consumption and frequent contact with plastic products (such as toys and bottles) that contain BPS. Further studies are needed to assess the sources of BPS exposures in humans.

The urine samples collected from Albany, New York, originated mainly from Caucasians and Asians. Caucasians had higher urinary BPS concentrations ($n = 17$; GM: 0.333 ng/mL and 0.358 μg/g Cre) than did Asians ($n = 14$; 0.262 ng/mL and 0.250 μg/g Cre), although the difference was not statistically significant ($p > 0.05$; Figure 2). Further studies with large sample sizes are needed to elucidate the influence of demographic features on BPS exposures in humans.

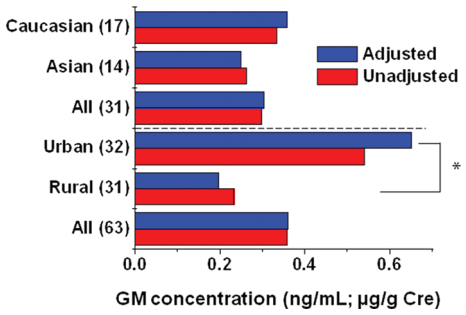

Figure 2. Comparison of BPS concentrations (ng/mL; μg/g Cre) in urine samples from Albany, New York, U.S. ($n = 31$) and Harbin, China ($n = 63$) in terms of ethnicity and domicile of residence. The numbers within parentheses on the *x*-axis represent the number of samples analyzed. * $p < 0.05$, one-way ANOVA.

Urban−Rural Differences in BPS Concentrations. Differences in urinary BPS concentrations for samples collected from urban ($n = 32$) and rural ($n = 31$) areas in Harbin, China, were examined. BPS was found in all urine samples collected from urban residents, at concentrations ranging from 0.108 to 3.16 ng/mL, whereas 25 of 31 (81%) urine samples from rural residents contained BPS at concentrations in the range of <LOQ to 1.74 ng/mL. The urinary GM and median concentrations (0.651 and 0.571 μg/g Cre) of BPS in urban residents were significantly higher than those (0.196 and 0.305 μg/g Cre) in rural residents ($p < 0.05$; Figure 2).

Human Exposure to BPS. The mean and median EDIs of BPS by the general populations in all eight countries collectively were 0.930 and 0.248 μg/day respectively (Table 2). Among the eight countries, the highest daily intakes of BPS (mean and median values) were estimated for Japan (3.47 and 1.67 μg/day), followed by the U.S. (1.48 and 0.316 μg/day), China (0.707 and 0.339 μg/day), and Kuwait (1.06 and 0.292 μg/day). The EDI values of BPS in Japan were approximately 1 order of magnitude higher than those estimated for Malaysia (mean and median: 0.180 and 0.122 μg/day) and Korea (0.154 and 0.023 μg/day; $p < 0.05$; Table 2). This can be explained by relatively high concentrations and detection frequency of BPS in urine samples from Japan (Table 1). The EDIs of BPS by the populations in the seven Asian countries were 1−2 orders of magnitude lower than the EDIs reported for BPA (Table 2).[11]

Table 2. Estimated Human Exposure Doses (μg/day) to BPS in Albany, New York, U.S., and Seven Asian Countries, in Comparison with Exposure Doses to BPA

BPS (this study)				
variable	*n*	mean ± SD	median	range
country				
USA	31	1.48 ± 4.51	0.316	0.017−25.1
China	89	0.707 ± 0.847	0.339	0.017−3.79
India	38	0.243 ± 0.340	0.084	0.017−1.41
Japan	36	3.47 ± 4.07	1.67	0.101−15.3
Korea	33	0.154 ± 0.544	0.023	0.017−3.16
Kuwait	30	1.06 ± 3.49	0.292	0.010−19.3
Malaysia	29	0.180 ± 0.270	0.122	0.017−1.47
Vietnam	29	0.278 ± 0.259	0.217	0.044−1.49
age				
children and adolescents (age <20)	33	0.457 ± 0.602	0.271	0.010−2.86
adults (age ≥20)	265	1.03 ± 2.68	0.258	0.017−25.1
gender				
male	152	1.30 ± 2.80	0.348	0.017−19.3
female	150	0.604 ± 2.17	0.186	0.010−25.1
all	315	0.930 ± 2.48	0.248	0.010−25.1
BPA (ref 11)				
variable	*n*	mean	median	range
country				
China	116	6.56	2.13	0.08−50.0
India	21	3.35	2.90	0.43−9.52
Japan	36	3.36	1.61	0.17−39.4
Korea	32	5.89	3.69	0.08−18.0
Kuwait	32	6.99	5.19	0.08−45.9
Malaysia	29	3.22	1.80	0.08−22.9
Vietnam	30	5.65	2.01	0.27−51.2
age				
children and adolescents (age <20)	47	2.58	1.16	0.03−13.6
adults (age ≥20)	249	5.28	2.21	0.08−51.2
gender				
male	153	5.85	2.58	0.08−50.0
female	143	5.12	2.22	0.08−51.2
all	296	5.50	2.39	0.08−51.2

It should be noted that several uncertainties exist in the assessment of exposure to BPS based on the measured urinary concentrations. The pharmacokinetics of BPS is not well understood, and we assumed that BPS and BPA have similar pharmacokinetics. Our discussion of the association of BPS concentrations with demographic features is tempered by the small sample size from individual countries. Thus, further studies with large sample sizes are needed.

Studies on the sources, pathways, and fate of BPS in the environment are very limited. To our knowledge, this is the first

study on the occurrence of BPS in human urine from the U.S. and Asian countries. Our results indicate that human exposure to BPS is ubiquitous. Relatively higher concentrations of BPS found in urine samples from Japan and the U.S. than in other countries suggest widespread use of BPS as a replacement for BPA in various applications in these countries. The median estimated daily intake of BPS was 0.009 and 0.004 μg/kg bw/day for children and adults (based on nominal body weights of 30 and 60 kg), respectively, which is below the reference dose of 50 μg/kg bw/day set for BPA by several environmental organizations, including the U.S. EPA.

■ ASSOCIATED CONTENT

Supporting Information

Information on age and gender of donors of urine samples, Pearson correlation analysis between unadjusted and creatinine-adjusted BPS concentrations, and representative total ion chromatograms of a standard mixture and a urine sample. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank all the donors for kindly providing urine samples for this study. We thank Madam Suad Al-Hooti (Kuwait Institute for Scientific Research) for the collection of urine samples in Kuwait, Drs. Tu Binh Minh and Nguyen Hung Minh (Vietnam Environment Administration) for the collection of samples in Vietnam, and Mr. Perianna Gounder Kurunthachalam for the collection of samples in India. This study was funded by a grant (1U38EH000464-01) from the Centers for Disease Control and Prevention (CDC, Atlanta, GA) to Wadsworth Center, New York State Department of Health, where the study was conceived and performed. Its contents are the sole responsibility of the authors and do not necessarily represent the official views of the CDC. A part of the study was supported by the National Natural Science Foundation of China (20907039) and the Department of Science and Technology of Shandong Province (BS2009HZ003).

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