Environmental Research 109 (2009) 629–633

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Bisphenol A levels in blood and urine in a Chinese population and the personal factors affecting the levels ☆

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ARTICLE INFO

Article history:
Received 25 November 2008
Received in revised form
2 April 2009
Accepted 8 April 2009
Available online 8 May 2009

Keywords:
Bisphenol A
Exposure level
Urine
Serum
Personal factor

ABSTRACT

The objective of the study was to describe the background bisphenol A (BPA) levels in urine and serum of a Chinese population without occupational exposure and to examine the personal characteristics influencing these levels. Workers from 10 factories and their family members were recruited and their peripheral blood and spot urine samples were collected. The conjugated and free BPA of the samples was assayed with high-performance liquid chromatography. The exposure levels were checked with 2-independent-samples test, and the potential personal factors influencing exposure levels were analyzed using nonlinear correlation. Of the total of 952 subjects participating in the study, urine and blood samples were taken from 97% and 93% of them, respectively. The detectable rates were 50% for urine samples and 17% for serum samples, given the detection limit of 0.31 μg/L for urine and 0.39 μg/L for serum. The arithmetic mean (AM) and geometric mean (GM) of non-creatinine-adjusted urinary BPA level were 10.45 and 0.87 μg/L, which became 24.93 and 0.38 μg/g Cr after the creatinine level was adjusted; serum BPA levels were 2.84 μg/L (AM) and 0.18 μg/L (GM). Males and those with smoking habit had higher biological burden of BPA. The results indicated that half of the study subjects had detectable BPA in their urine samples. BPA levels were influenced by gender and smoking status. The sources of non-occupational BPA exposures should be explored.

1. Introduction

Bisphenol A (BPA) is a high-volume (>6 billion pounds per year) production chemical mainly used to make epoxy resins, polycarbonate plastic, polysulfones, and polyurethanes (Chapel Hill bisphenol A expert panel consensus statement, 2007; Kang et al., 2006). BPA is a suspected environmental endocrine disruptor that has been shown to interfere with the reproductive system. It may increase carcinogenic risk, cardiovascular diagnosis and diabetes in humans (Dodds and Lawson, 1936; Welshons et al., 2006; Huff, 2003; Lang et al., 2008). BPA has been demonstrated to be both estrogenic and antiandrogenic, leading to the decrease in sperm production in humans (Toppari et al., 1996) and abnormal development of puberty in experimental animals (Savabieasfahani et al., 2006). The general population is likely to be exposed to BPA in daily life by using BPA-containing products such as baby bottles, inner coating of food cans, water containers and dental sealants (Roy et al., 1997). BPA was found in the general indoor air samples with the level of 2–8 ng/m^3 (Silbergeld and Flaws, 2002). BPA was also detected in indoor air of children's daycare centers and/or homes, hand wipes, solid food, and liquid food samples (Wilson et al., 2007). It was reported that the average urine BPA level of different populations had a range of 0.11–3.2 ng/mL with a detection rate of 52–100%, while BPA levels in serum were between 0 and 2.5 ng/mL (Vandenberg et al., 2007). So far, no study has been conducted in China on BPA exposure levels. It is of public health importance to have more information on the internal dose of BPA in the human body and to understand the nature of BPA exposure. The present study assesses the BPA levels in urine and serum of a Chinese group without occupational exposure and examines the personal characteristics potentially influencing these background BAP levels.

2. Materials and methods

2.1. Subjects

As a part of a research project of reproductive effects of BPA on exposed workers, the study was approved by the Institutional Review Board (IRB) of Fudan University, Shanghai, China. Besides

☆ This study was supported by a grant from the U.S. National Institute of Occupational Safety and Health (NIOSH) (R01 OH007580).
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doi:10.1016/j.envres.2009.04.003

all workers from 10 factories of chemical or machinery industries in the east and middle mainland China, their spouses and their children were invited to participate in this study. After obtaining the informed consents, workers and their family members were asked to provide information on demographic data, lifestyle habits (smoking and drinking), and educational level using a standardized questionnaire. For the purpose of this study, the eligible participants referred to those without occupational BPA exposure that should be confirmed by worksite visiting or consulting the products, raw materials, processing and their job categories. Anyone who had a dental sealant application within 1 year was excluded (Joskow et al., 2006). All subjects were asked to contribute 1 mL venous blood and 5 mL spot urine specimens during the day time of weekdays. The serum was separated from blood cells by centrifuging at 3000 rpm for 15 min. All the biological samples were stored at −70 °C before high-performance liquid chromatography (HPLC) analysis.

2.2. Analysis of BPA in urine and serum

Total BPA (conjugated and free) in urine and serum were measured with HPLC based on the modified methods of Yang et al. (2003). In brief, the reaction mixtures of phosphorous acid buffer, β-glucuronidase (Sigma) and sample aliquots in glass tubes were incubated for hydrolyzation, and then were extracted twice with ether (HPLC grade, Dikma). The supernatants were collected and evaporated with nitrogen gas. The residue was dissolved in 60% acetonitrile (HPLC grade, Dikma) and analyzed by HPLC on the following parameters: column, Inertsil ODS-3, 4.6mm × 250 mm, 5 μm; mobile phase A and B, acetonitrile/water (40:60, v/v), equivalent grade; flow: 1.0 mL/min; FLD, excitation wavelength 275 nm, emission wavelength 300 nm. Water was from Millipore Super-Q Plus water purification system (Bedford, MA).

The BPA fraction was confirmed by the standard BPA (HPLC grade, Shanghai Yuanxing Company) with the same HPLC base. The limit of detection (LOD) was calculated with the method recommended by EPA (EPA, 2004). The LODs of BPA in urine and serum were 0.31 and 0.39 μg/L, respectively, which were similar to those reported at 0.1–1.14 μg/L in some studies (Calafat et al., 2005; Catafat et al., 2008; Engel et al., 2006), but substantially higher than those used in other studies at 0.012–0.026 μg/L (Vandenberg et al., 2007).

2.3. Statistical analysis

There were large variations in BPA concentrations in the biological samples, and the data were not normally and log-normally distributed. We used the median, arithmetic mean (AM) and geometric mean (GM), 25th and 75th percentiles (P25th–P75th) to describe the results. A value equal to the LOD divided by 2 or by the square root of 2 was used, respectively, in the computation of AMs and GMs to substitute the measurements under LOD. To check the extent of spot urinary BPA levels influenced by sample timing, we reported both the urinary BPA concentrations adjusted or unadjusted by creatinine.

Age was categorized into 5 groups ($\leqslant$20, 21–30, 31–40, 41–50, $>$50). Educational level was categorized into 4 groups ($\leqslant$junior middle school, $\leqslant$senior middle school, $\leqslant$junior college, university and above). Smoking was defined as lifetime smoking of at least 100 cigarettes up to the interview date and dichotomized (yes/no). Drinking was defined as lifetime drinking of alcohol beverages (beer, wine, and liquor) at least once a week for more than 6 months and also dichotomized (yes/no). Most of the workers were the young migrants who did not have children or their children were not with them when the investigation was taken, resulting in only 59 subjects under 18 years old being recruited. Information on experiences of smoking and drinking habit from subjects younger than 18 years old were not collected, as we doubted the accuracy of this piece of information.

The participation rate and the detectable rate of the biologic samples were tested with the χ^2 test by personal characteristics, including gender, age group, educational level, smoking, and drinking habits. The biological exposure levels were compared with the Mann–Whitney U Two-Independent-Samples Test. Kendall's tau_b of nonparametric analysis was used to check the rank correlation between BPA concentration and age or educational level. Personal factors potentially affecting exposure levels were analyzed with multivariate nonlinear regression by including the significant variables obtained from the univariate analyses. The correlation of BPA levels in urine and serum was checked with Spearman correlation analysis. The p-value was set at 0.05, two-tailed.

2.4. Quality control

Well-trained field investigators and HPLC operators with professional experience in occupational hygiene and chemical analysis were involved in this project. Several pilot studies were performed before conducting the fieldwork. The containers of the biological sample were plastic tubes and were reported to be BPA-free by the supplier. A simulative test was performed to check if any difference in BPA level of the same urine sample was detected between that stored in the plastic tube and the glass tube at 4 °C for 8 h by using HPLC analysis. The results did not show any significant difference, indicating less likely the biological samples being contaminated by BPA from the containers. Blank samples were randomly included during each HPLC analysis and no BPA was detected. A urine sample of defined concentration at 4.5 mg/L was included in parallel analysis for 5 times during every HPLC analysis, and the concentrations were identified accurately.

3. Results

3.1. Characteristics of subjects

We had a total of 952 eligible subjects being recruited in the study, giving a participating rate of 98%; 21 subjects refused to participate because they were unwilling to provide any biological samples. The mean age of the participants was 33.9±9.3 years, and 45.5% of them were males (Table 1). Ninety-seven percent of the participants provided urine samples and 93% provided serum samples. The participation rates for providing urine and serum samples were not significantly different by gender, age, educational level, and lifestyles.

3.2. Urinary BPA concentration in the subjects

BPA was detected in 50% of the urine samples from the subjects (Table 2). The detection rate in males (58%) was significantly higher than in females (48%) ($p<0.01$). People $\leqslant$40 years old had higher detection rates than people $>$40 years old. No significant differences existed for the rates of the people in age groups below 40 years, despite people $\leqslant$40 groups had higher detectable rate than that $>$50 years old. Subjects with educational level above junior middle school had higher detection rate than those with lower education level. Both smoking and drinking were significantly associated with higher BPA detection rates in urine samples.

Without the adjustment of creatinine, the median, AM and GM of urine BPA level of our participants were <LOD, 10.45 and 0.87 μg/L, with P25th–P75th between <LOD and 5.26 μg/L. Older subjects, especially those aged >40 years old, had lower BPA levels in urine (Kendall's rank correlation coefficient = −0.09, $p<0.01$), while males and subjects with significantly higher educational level had higher BPA levels (Kendall's rank correlation coefficient = 0.087, $p<0.01$). Both smoking and drinking were significantly associated with higher BPA levels in urine. GM was closer to the median but was much lower than to the AM. In general, the groups with higher detection rates of urinary BPA had higher exposure levels according to GM or the median; however, it was not always the case for AM.

The median, AM and GM of the creatinine-adjusted BPA levels in urine were <LOD, 24.93 and 0.38 μg/g Cr. However, the creatinine-adjusted urinary BPA levels were not associated with educational levels (the correlation coefficient = −0.037, $p=0.170$).

Table 1
Characteristics of subjects and participation rate for biologic samples.

	Number of subjects	Participation rate	
		Urine sample	Serum sample
Gender			
Male	433	0.97	0.93
Female	519	0.97	0.93
Age (years)			
⩽20	67	0.97	0.88
21–30	232	0.96	0.90
31–40	440	0.98	0.96
41–50	165	0.97	0.93
>50	48	0.96	0.88
Education			
⩽Junior middle school	281	0.96	0.93
⩽Senior middle school	501	0.96	0.93
⩽Junior college	134	1.00	0.95
University and above	36	1.00	0.97
Smoking			
No	596	0.97	0.93
Yes	297	0.97	0.93
Drinking			
No	763	0.98	0.94
Yes	130	0.92	0.91
Total	952	0.97	0.93

3.3. Serum BPA concentration of general population

BPA was detected in 17% of serum samples from the study subjects (Table 3). The detection rate in male subjects was significantly lower than that in females ($p<0.01$). The younger people had higher detection rates than the older ones (correlation coefficient = −0.094, $p=0.000$). Educational level did not influence the detection rate of BPA in serum. Both smoking and drinking were significantly associated with higher detection rates in serum samples.

The median, AM and GM of serum BPA level in all the participants were <LOD, 2.84 and 0.18 μg/L, respectively. The serum BPA levels in the male group were significantly higher than in the female group. Older people had lower BPA levels in serum (Kendall's rank correlation coefficient = −0.09, $p<0.01$). Smoking was significantly associated with higher BPA levels in serum, but drinking was not. The groups with higher detection rates of serum BPA always had higher exposure levels for GM but not for AM, with the exception of the gender groups. GM of every group (Table 3) was lower than AM. As the detection rates in most groups were under 25%, the median and most of the P25th–P75th were <LOD.

3.4. Factors affecting biologic burden of BPA

Gender and smoking remained the significant influencing factors associated with creatinine-adjusted urinary BPA levels or

Table 2
Not creatinine-adjusted (μg/L) and creatinine-adjusted (μg/g Cr) urinary BPA concentration in the subjects[a].

	Number	Detection rate	Median	Arithmetic mean of not adjusted/ adjusted level	Geometric mean of not adjusted/ adjusted level	P75th of not adjusted/adjusted level
Gender						
Male	419	0.58	1.46 (1.43)	14.68 (40.18)	1.41 (0.72)	10.60 (14.18)
Female	503	0.44	<LOD (<LOD)	6.92 (12.23)	0.58 (0.23)	2.09 (4.50)
Age (years)						
⩽20	65	0.57	0.70 (0.60)	6.82 (40.48)	0.78 (0.92)	2.09 (3.75)
21–30	222	0.55	0.42 (0.94)	10.58 (15.05)	0.96 (0.53)	5.64 (7.59)
31–40	429	0.54	0.57 (0.69)	11.21 (31.03)	1.06 (0.47)	7.59 (8.84)
41–50	160	0.39	<LOD (<LOD)	7.44 (13.24)	0.64 (0.24)	4.73 (8.51)
>50	46	0.15	<LOD (<LOD)	18.31 (34.38)	0.26 (0.06)	LOD (LOD)
Education						
⩽Junior middle school	271	0.41	<LOD (<LOD)	9.85 (23.33)	0.61 (0.28)	2.53 (8.07)
⩽Senior middle school	481	0.53	0.36 (0.54)	11.38 (31.06)	0.98 (0.43)	6.00 (7.66)
⩽Junior college	134	0.53	0.31 (0.42)	9.85 (11.51)	0.99 (0.41)	6.22 (8.18)
University and above	36	0.69	1.91 (2.25)	4.75 (5.00)	1.39 (0.76)	7.80 (8.41)
Smoking						
No	577	0.44	<LOD (<LOD)	8.86 (14.00)	0.59 (0.24)	2.25 (4.44)
Yes	287	0.60	2.89 (3.57)	14.21 (43.02)	1.88 (0.94)	15.59 (16.56)
Drinking						
No	745	0.47	<LOD (<LOD)	10.51 (24.38)	0.78 (0.33)	4.24 (7.06)
Yes	119	0.62	1.97 (2.78)	11.47 (19.98)	1.65 (0.97)	11.9 (43.66)
Total	922	0.50	<LOD (<LOD)	10.45 (24.93)	0.87 (0.38)	5.26 (7.9)

[a] The P25ths for all groups were at <LOD.

Table 3
Serum BPA concentration in the subjects (μg/L)[a].

	Number	Detection rate	AM	GM
Gender				
Male	404	0.13	3.81	0.20
Female	482	0.21	2.03	0.16
Age (years)				
⩽20	59	0.29	1.12	0.24
21–30	208	0.24	3.88	0.22
31–40	423	0.14	2.32	0.17
41–50	154	0.13	0.75	0.15
>50	42	0.12	13.14	0.19
Education				
⩽Junior middle school	260	0.17	2.85	0.18
⩽Senior middle school	464	0.18	3.56	0.19
⩽Junior college	127	0.15	0.86	0.16
University and above	35	0.20	0.56	0.18
Smoking				
No	557	0.12	2.40	0.16
Yes	277	0.18	3.21	0.19
Drinking				
No	716	0.14	0.97	0.16
Yes	118	0.17	3.27	0.18
Total	886	0.17	2.84	0.18

The P75ths for all groups were at <LOD, except for the ⩽20 years old group at 1.01 μg/L.
[a] Medians of all the groups were <LOD.

Table 4
Nonlinear regression analysis on urinary creatinine-adjusted BPA concentration and serum BPA concentration.

	Urine			Serum		
	Beta[a]	*T*-value	*p*-Value	Beta[a]	*T*-value	*p*-Value
Model (F)	0.014[b]	2.96	0.02	0.08[b]	2.75	0.02
Variable						
Being male	0.14	3.07	0.02	0.12	2.36	0.02
>40 yr old	0.01	0.13	0.90	0.03	0.88	0.38
Smoking	0.23	2.13	0.03	0.11	2.13	0.03
Drinking	0.10	0.83	0.41			

[a] Standardized regression coefficient.
[b] R^2.

blood BPA levels in the multivariable analysis (Table 4). Being a female and non-smoker were associated with lower exposure levels.

The Spearman correlation coefficient was 0.144 ($p<0.01$) for the relationship between creatinine-adjusted urinary BPA concentration and serum BPA concentration.

4. Discussion

The production and consumption of BPA is growing dramatically around the world, with an annual increase of 6–8% (Gao, 2003). The annual product of BPA in China was 3200 ton, accounting for 1.1% of the output over the world and 3.3% in America in 2003. In developed countries, BPA is mainly used as a raw material in polycarbonate plastic and epoxy resins (e.g., 67.56% and 25.5%, respectively, in America), whereas in China 84.15% BPS was consumed in epoxy resins and 1.14% in polycarbonate plastic (Gao, 2003). Furthermore, over 40% epoxy resins in China was raw material of paints. The different usage of BPA and BPA-contained productions may result in varied exposure routines. The Chinese population might have more chances to be exposed to BPA by inhalation but fewer chances by ingestion than people in the developed countries.

For urinary BPA, the detection rate among our study subjects was 50%, and this prevalence was less than that reported in many studies (ranging from 52% to 100%) in other countries (Vandenberg et al., 2007). However, a study of 7 males and 12 females in Germany did not detect BPA in their urine samples (Wolfgang et al., 2005). The levels of urine BPA in our study subjects varied widely, with a GSD of 8.75 μg/L, which was similar to that reported by a Korean study (GSD = 8.32 μg/L (Yang et al., 2003). The AM (10.45 μg/L) of urine BPA in our subjects was much higher than those reported in other studies (2.0–2.82 μg/L) (Roy et al., 1997). On the other hand, the GM (0.87 μg/L) in the current study was lower than that reported in some studies, e.g., a GM of 9.54 μg/L was reported among Koreans (Yang et al., 2003), and GMs of 1.3 and 2.6 were reported in the NHANES III (Calafat et al., 2005) and NHANES 2003–2004 (Catafat et al., 2008) studies, respectively. These differences could be due to the different exposure levels, LODs (0.012–0.36 μg/L in the various studies), and the sample timing (Catafat et al., 2008).

The association between urinary BPA level and gender has not been consistently reported in previous studies. We found that the female subjects had significantly lower urinary BPA concentrations than the males. Taking into account the fact that most of the urinary BPA is glucuronide-conjugated, this observation was consistent with the results from Korean studies (Kim et al., 2003). The median and GM of creatinine-adjusted urinary BPA levels in the present study were much lower than those reported in the US (<LOD and 0.38 μg/g Cr in the present study for median and GM, while 2.5 and 2.6μg/g Cr in the US reports) (Catafat et al., 2008).

In the univariable analysis, the urinary BPA levels and its detectable rate decreased significantly in the older age groups, but the association did not remain significant in the multivariable analysis. A lack of statistically significant association in the multivariable analysis might partly be explained by the small sample size in some age groups, e.g., ⩽20 years old (65, about 5.5% of this population) and >50 years old (46, about 5.0% of the population). We found an increased non-creatinine-adjusted urinary BPA level (GM only) in the higher educational level groups. Assuming that educational level was associated with income, it is expected that this finding would be different somewhat from the results of NHANES (Catafat et al., 2008), in which a lower urinary BPA lever was obtained in the higher income groups. However, the educational levels were not associated with creatinine-adjusted urinary BPA level. Consistent with the study by Catafat et al. (2008), we found that smoking was a significant factor affecting urinary BPA levels in our non-occupational exposed population.

For serum BPA, the AM among women in the present study was 2.03 μg/L, which was similar to a Japanese study involving 30 healthy premenopausal women (2.0 μg/L) (Yumiko et al., 2002). Serum BPA levels in the male were significantly higher than in the female in the present study, which was similar to that found in a Korean study of 25 subjects (male vs. female: 1.49 vs. 0.64 ng/ml) (Toru and Osamu, 2002); however, it should be noted that the detection rate of serum BPA was generally lower in our study (17%) than some other studies (up to 100%) (Vandenberg et al., 2007). Such difference might be related to the sensitivity of the analysis method (0.39 μg/L in the present study vs. 0.01–0.30 μg/L in some other studies). It is interesting to show that we are the first to report that the gender and smoking were the significant influencing factors for serum BPA levels, and such finding has never been reported by other studies worldwide.

We found a close relationship between the urinary BPA level and serum BPA level. However, this finding was very preliminary

and the interpretation was limited by the low detectable rate in the serum samples. Nevertheless, taking into account the higher concentration and detection rate of BPA in urine samples than in serum, urinary BPA is suggested as the preferred indicator for biological exposure assessment.

There were some limitations in the study. First, the lack of information regarding environmental sources for our subjects, e.g. water source, plastic bottles, water container, etc., prevented us from discovering the sources of BPA in the Chinese population. Secondly, the subjects were the workers and their family members from the factories in the central and east China and most of them aged from 30 to 50 years old, which perhaps could not well represent the general Chinese population. Thirdly, due to the limitation of the apparatus and laboratory methods, the LODs of our study were relatively high compared to some other studies, which might lead to low detection rates.

5. Conclusion

Results of the present study showed that half of the study subjects had detectable BPA in urine and 17% in serum. BPA level in urine and serum was higher in males and in those with smoking habit. The sources of non-occupational BPA exposures of the general Chinese population should be further explored.

Funding sources

National Institute of Occupational Safety and Health (NIOSH) of America (R01 OH007580).

IRB approval

The study was approved by the Institutional Review Board of Fudan University, Shanghai, China on October 25, 2007 (No. IRB #04-08-00019).

Acknowledgments

We appreciate the many suggestions on the manuscript provided by Dr. Yu Tak Sun Ignatius and Dr. TSE Lap Ah Shelly of the Chinese University of Hong Kong University.

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