Asian Biomedicine Vol. 9 No. 3 June 2015; 363 - 372 DOI: 10.5372/1905-7415.0903.405

Brief communication (Original)

Urinary bisphenol A detection is significantly associated with young and obese Thai children

Sopon Pornkunwilai[a], Wichit Nosoongnoen[b], Chutima Jantarat[c], Suttipong Wachrasindhu[a], Vichit Supornsilchai[a]
[a]*Division of Endocrinology, Department of Pediatrics, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand*
[b]*Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand*
[c]*School of Pharmacy, Walailak University, Nakhon Si Thammarat 80161, Thailand*

Background: Bisphenol A (BPA), a xenoestrogenic monomer, is one of the most common industrial chemicals used in epoxy coatings for canned food and other consumer items. There is only limited information regarding the potential health risks from BPA exposure in children and adolescents from Asian countries.
Objective: To detect and determine urinary BPA concentrations, and identify possible association between urinary BPA levels, demographic characteristics, and BPA exposure risks in Thai children and adolescents.
Methods: A cross-sectional study was conducted in 376 children and adolescents aged 3–18 years from kindergarten, elementary, and middle schools in Bangkok, Thailand. Urinary concentrations of total BPA were determined by liquid chromatography tandem mass spectrometry (LC–MSMS). Anthropometric data and questionnaires regarding BPA exposure risks were collected.
Results: BPA was detected in 283 of 376 urine samples (75.3%) with a median adjusted BPA 0.53 μg/g creatinine (range 0.04–1.12). Thirty-one participants (9%) were overweight and 39 (11%) were obese. The BPA detection rate was significantly higher in obese children (OR 3.42, 95% confidence interval (CI) 1.18–9.95, $P = 0.02$) compared with children of normal weight. BPA was detected more often in younger children (3–6 years) when compared with children (6–10 years) and adolescents (10–18 years). There were no significant association between BPA levels and other demographic data or BPA exposure risks.
Conclusions: BPA exposure in Thai children and adolescents may be lower than exposure in children from the United States, some European nations, and other Asian countries. Obese and younger children were significantly associated with BPA detection.

Keywords: Bisphenol A, LC–MSMS, liquid chromatography tandem mass spectrometry, obesity, overweight

Bisphenol A (BPA), a xenoestrogenic monomer, is a common industrial chemical and is used to synthesize polycarbonate plastic polymers, which are applied to manufacture of various products such as compact discs, automobile parts, plastic water and baby bottles, plastic dinnerware, eyeglass lenses, toys, and thermal paper, and epoxy resin linings in cans for food products [1]. Over 3 thousand million kilograms of BPA are produced each year. Recent studies have shown that dietary ingestion is a major route (99%) of human exposure to BPA contamination, especially from canned foods [2, 3]. Other routes are microwave containers, soft drinks, smoking, alcohol consumption, dental sealants [4], medical procedures [5], and plastic tubing [6]. BPA was detected in about 93%–100% of children and adolescents in Northern America, some European nations, Egypt, Australia, and Asian countries [7-17]. The only report from Thailand found that BPA was detected 52.8% in serum samples in adults [18]. Negative health outcomes have been associated with bisphenol A. BPA is postulated to alter pancreatic β-cell functions [19, 20] and thyroid hormone pathways [18]. There have been links with insulin resistance [20-21], type 2 diabetes mellitus [6, 22, 23], obesity [24-30], coronary heart disease [31], coronary artery stenosis [32], precocious puberty in girls [33], and behavioral problems including anxiety, depression, and hyperactivity [34, 35]. Obesity is an increasing health problem in Thailand. Obesity is related with comorbidities, such as metabolic and cardiovascular diseases [36]. The prevalence of

Correspondence to: Vichit Supornsilchai, Division of Endocrinology, Department of Pediatrics, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand.
E-mail: vichit.s@chula.ac.th

obesity in Thai children is 7.9%–10.8% and the trend has been increasing [37-39]. Obesity is a complex, multifactorial disease and its etiology involves the interaction between both genetic and environmental factors including endocrine disruptors (EDs). An association between urinary BPA concentrations and obesity has previously been reported [24-30]. To our knowledge, the present study is the first study of BPA exposure in Thai children and adolescents using the standardized and highly sensitive technique of liquid chromatography tandem mass spectrometry (LC–MSMS) to determine BPA in urine. Urine is an appropriate specimen with which to determine BPA exposure because BPA and its metabolites are present in urine for several weeks or months [40, 41]. BPA is rapidly eliminated from plasma within 24 hours after ingestion [41].

Material and methods

Participants

This cross-sectional study was conducted between September 2012 and January 2013. Participants were recruited from two schools, one kindergarten–elementary school and one middle school in the Patumwan District of Bangkok. Consent forms were signed by the parents of the 482 students we attempted to recruit for the study. Ninety-two students were excluded from the study because of incomplete consent or for failing to return the questionnaire. Fourteen students were excluded because of an inadequate amount of urine submitted for analysis.

Written informed consent was obtained from the parents of all participants and ascent was obtained from all students older than 7 years after they were informed of the study protocol and procedures including the urine specimen collection process. The study was approved by the Institutional Review Boards of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB 050/56).

Data collection

All data were collected at the date of urine collection. The questionnaire was divided into 2 parts, which included demographic data and possible exposure risks. Demographic data included age, sex, current residence, eating habits, caregiver education, family income, awareness of pubertal status, and total daily hours of television watching. BPA exposure risks included junk food, canned food, and bottled milk consumption, use of plastic containers for food and water, use of microwave to heat plastic food containers and plastic toys. The frequency of exposure was classified into 6 categories, including "never", "at least once per month", "once per month", "once per week", "more than 2 days per week" and "at least once a day".

Anthropometric measurement

Body weight (kg) and height (cm) were measured by trained teachers. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Age- and sex-standardized BMI *z* scores were adjusted using CDC 2000 growth charts. Overweight and obesity levels were categorized as BMI *z* score of 1.036 or greater (85^{th} percentile for age and sex) and 1.64 or greater (95^{th} percentile), respectively [42].

Urine sample collection

Morning urine samples (40–50 mL) were obtained from students in BPA free polypropylene tubes. The collected urine samples were immediately transported to a laboratory and stored at –80°C until analysis [43].

Analysis of BPA

For each urine sample, total urinary BPA concentrations (free plus conjugated species) were analyzed by solid-phase extraction (SPE) coupled with high-performance liquid chromatography tandem mass spectrometry (HPLC–MS/MS). The lower limit of quantification (LLOQ) of BPA was 0.05 ng/mL.

Urine sample preparation for BPA analysis

Urine samples (500 µL) were fortified with 50 ng/mL of d_{16}-BPA as an internal standard and supplemented with 100 µL of ammonium acetate buffer (0.1 M, pH 6.5) and 1,200 units (12 µL) of glucuronidase/sulfatase. The mixture was incubated at 37°C for 3 h and then centrifuged at 13,000 rpm for 10 min before clean up by solid-phase extraction (SPE) using an Oasis HLB cartridge (60 mg/3 mL; Waters, Milford, MA). Cartridges were preconditioned with 5 mL of methanol and 5 mL of deionized (DI) water. After loading samples, the cartridge was washed with 2 mL of 0.1 N HCl and 5 mL of 10% methanol in water and eluted with 3 mL of methanol. The elute was concentrated to 150 µL using centrifugal vacuum concentrator (MiVac, Genevac Inc, NY, USA) and subjected to HPLC–MS/MS analysis.

Quantitation of BPA was based on calibration curves of 8 concentration points: 0.05, 0.1, 0.5, 1, 5, 10, 20, and 50 ng/mL obtained after fortification with d_{16}-BPA as the internal standard followed by extraction using the same method as described for the preparation of urine samples.

Instrumental analysis

Quantification of BPA was performed using an Agilent 6490 HPLC–MS/MS (Agilent Technologies Inc, Santa Clara, CA). The chromatographic column used was Zorbax RRHD Eclipse Plus C_{18} (2.1 mm × 50 mm, 1.8 μm; Agilent Technologies Inc). The mobile phase was 0.05% acetic acid in DI water and acetonitrile (60:40). The system was run with an isocratic elution at 0.4 mL/min. The column temperature was 30°C and injection volume was 4 μL. The entire analysis took 3.5 min. The MS/MS was operated in the electrospray negative ion multiple reaction monitoring (MRM) mode. Optimal conditions were: gas temperature 200°C, gas flow 14 L/min, Nebulizer 30 psi, sheath gas temperature 350°C, sheath gas flow 11 L/min, and ion spray voltage –3,500 V. All channels were monitored with a 100 ms dwell time. Mass transitions and collision energies 227 → 212 and –17 V; and 241 → 223 and –18 V were monitored for BPA and d_{16}-BPA, respectively.

Analysis of urine creatinine

Urine creatinine (Cr) was analyzed using the Jaffe method with a Beckman Coulter reactive in AU5400 (IZASA) (Beckman-Coulter Inc). Each urinary BPA concentration in ng/mL was adjusted to g/g Cr.

Daily intake of BPA

Daily intake of BPA was estimated using the following equation; Daily intake (μg/day) = Urinary BPA concentration (μg/L) × urine excretion rate (L/day). Daily urinary excretion rates were reported to be 500, 700, and 1,200 mL for ages below 5, 6–11, and 12–18 years, respectively [44].

Statistical analysis

A chi-squared test was used to evaluate dichotomized variables, while an unpaired *t* test and ANOVA were used for continuous variables. Logistic regression with a 95% confidence interval was used to estimate the odds ratio (OR) of variables for a degree of BPA association. Statistical significance was established at $P < 0.05$ and power at 80%. All statistical analyses were conducted using SPSS software version 17.

Results

We included 376 participants in the study (193 boys and 183 girls). Their mean age was 10.36 ± 3.39 years (range 3.58–17.17 years). BPA was detected at a level of more than 0.05 ng/mL in 283 (75.3%) of the 376 urine specimens. The overall median concentration of urinary BPA was 0.68 ng/mL (IQR 0.06–1.48; maximum concentration of 8.75) and the median concentration of creatinine-adjusted BPA concentration was 0.53 (IQR 0.04–1.12). In boys, the median concentrations of BPA and adjusted BPA were 0.78 (0.23–1.72) ng/mL and 0.54 (0.151.18) μg/g Cr, respectively. In girls, the median concentrations of BPA and adjusted BPA were 0.59 (0–1.31) ng/mL and 0.5 (0–1.02) μg/g Cr, respectively (**Table 1**).

The mean estimated daily exposure of BPA was 1.04 ± 1.46 μg/day as shown in **Table 1**. Urinary BPA levels were not associated with age, sex, family income, or other variables including BMI. Urinary BPA levels were not different between age categories. Dietary variables, such as junk food, canned food, bottled milk consumption, use of plastic containers for food and water, use of microwave to heat plastic food containers, and plastic toy play, were not associated with urinary BPA levels (data not shown). Median BPA levels were 0.67 (0–1.48), 0.62 (0–1.13), and 0.78 (0.39–1.7) ng/mL in normal weight, overweight, and obese children, respectively. Estimated daily intake was 0.5 (0–1.32), 0.45 (0–1.03), and 0.65 (0.3–2.04) in normal weight, overweight, and obese children, respectively.

The prevalence of overweight and obese children in this study were 9% and 11.3%, respectively. Detection rates were higher in children 3–9 years of age than in the adolescents, and higher in obese children than those that were not obese (**Table 2**). Family incomes were not significantly associated with BPA detection using logistic regression analysis. By contrast, obesity was significantly associated with BPA detection with an OR of 3.42 (95% CI: 1.18–9.95, $P = 0.02$) (**Table 3**). When considering urinary BPA levels (ng/mL or μg/g Cr), there was no significant difference between BPA levels in normal weight, overweight, and obese children (**Table 4**).

Table 1. Urinary bisphenol A (ng/mL), creatinine adjusted bisphenol A (μg/g Cr), and estimated daily intake (μg/day) by ages, genders, family income, and body mass index

Characteristics	Adjusted urinary bisphenol A (μg/g Cr)		Estimated daily intake (μg/day)	
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
Age (years)				
3.01–6.00	1.21 ± 1.53	0.70 (0–1.90)	0.55 ± 0.79	0.28 (0–0.66)
6.01–10.00	0.97 ± 1.43	0.71 (0–1.10)	0.67 ± 0.86	0.43 (0–0.87)
10.01–18.00	0.78 ± 1.07	0.45 0.13–0.98)	1.42 ± 1.79	0.80 (0.18––2.04)
Total	0.90 ± 1.28	0.53 (0.04-1.12)	1.04 ± 1.46	0.55 (0.06–1.48)
Sex				
Male	0.90 ± 1.09	0.54 0.15–1.18)	1.15 ± 1.49	0.60 (0.20–1.54)
Female	0.91 ± 1.45	0.50 (0–1.02)	0.92 ± 1.41	0.44 (0–1.09)
Family income (EUR/month)				
<453	0.88 ± 1.15	0.53 (0.04–1.14)	0.99 ± 1.36	0.55 (0.040–1.25)
453–906	0.74 ± 0.97	0.41 (0–0.97)	1.09 ± 1.86	0.35 (0–1.43)
>906	1.59 ± 2.44	0.71 (0.35–0.31)	1.46 ±1.35	0.76 (0.41–.34)
Body mass index				
Normal weight	0.91 ± 1.35	0.51 (0–1.09)	0.98 ± 1.39	0.50 (0–1.32)
Overweight	0.65 ± 0.96	0.36 (0–0.76)	1.14 ± 2.18	0.45 (0–1.03)
Obese	0.90 ± 1.03	0.71 (0.21.16)	1.24 ± 1.43	0.65 (0.30–0.04)

Table 2. Bisphenol A detection by age, sex, family income, and body mass index

	n (%)	Urinary bisphenol A (n, %)		*P*
		<0.05 ng/mL	≥0.05 ng/mL	
Age (years)				
3.01–6.00	40 (10.6)	15 (16.2)	25 (32.5)	0.048*
6.01–10.00	146 (38.8)	39 (41.9)	29 (37.7)	0.479
10.01–18.00	190 (50.6)	39 (41.9)	23 (29.8)	0.056
Sex				
Male	193 (51.3)	41 (44.1)	152 (53.7)	0.121
Female	183 (48.7)	52 (55.9)	131 (46.3)	0.121
Family income (EUR/month)				
<453	273 (74.0)	68 (73.9)	205 (74.0)	0.899
453–906	67 (18.2)	23 (25.0)	44 (15.9)	0.045*
>906	29 (7.8)	1 (1.1)	28 (10.1)	0.006*
Body mass index				
Normal weight	274 (79.7)	77 (86.5)	197 (77.3)	0.015*
Overweight	31 (9.0)	8 (9.0)	23 (9.0)	0.831
Obese	39 (11.3)	4 (4.5)	35 (13.7)	0.030*

*$P < 0.05$

Table 3. Association between body mass index, family income, and detection of bisphenol A in urine (%)

	OR	95% Confidence interval for OR	*P*
Family income (EUR/month)			
<453	1.00		1.00
453–906	0.64	0.36–1.13	0.12
>906	9.29	1.24–69.56	0.03*
Body mass index			
Normal weight	1.00		1.00
Overweight	1.12	0.48–2.62	0.79
Obese	3.42	1.18–9.95	0.02*

*$P < 0.05$, odds ratio (OR)

Table 4. Urinary bisphenol A level association with body mass index

	Body mass index			*P*	
	Normal (n = 724)	Overweight (n = 31)	Obese (n = 39)	Normal vs overweight	Normal vs obese
Urinary bisphenol A (ng/mL)	0.67	0.62	0.87	0.63	0.14
Adjusted bisphenol A (μg/g Cr)	0.51	0.36	0.71	0.30	0.19

P by Mann–Whitney *U* test

Discussion

To our knowledge, this is the first report of urinary BPA concentrations in Thai children and adolescents. The detection rate of BPA was 75.3% with a median concentration of 0.68 ng/mL. Sriphrapradang et al. reported the detection rate of BPA in Thai adults as 52.8% with a median serum BPA concentration of 0.33 ng/mL as determined by ELISA [17]. Although interesting, those findings cannot be compared directly with those in the present study because of the different samples and techniques used. However, our data suggest that BPA exposure may be higher in Thai children than in adults. A limitation of analyzing BPA in serum is the rapid degradation and elimination of BPA [40]. Therefore, urinary samples may provide more information regarding chronic BPA exposure [41]. The present study showed that Thai children and adolescents had lower levels of urinary BPA (0.68 vs 0.70–1.70 ng/mL) and detection (75.3% vs 79%–94.3 %) compared with data from Northern America, some European, Egypt, and other Asian countries [7-16]. The lowest observable adverse effect level was set in the 1980s at 50 mg/kg/day [45]. The European Food Safety Authority and U.S. Environmental Protection Agency (EPA) use the same "reference dose" or safe dose of 50 mg/kg/day [44] and this is calculated using the following formula "daily intake in μg/day is equal to urinary BPA concentration in μg/L × urine excretion rate in L/day". Daily urine excretion rates were reported to be 500, 700, and 1,200 mL for ages younger than 5, 6–11, and 12–18 years, respectively [44]. The median daily BPA intake was 0.55 (IQR 0.06–1.48) μg/day, which was lower than the reference safe dose by nearly a million fold. However, various molecular studies have shown a variety of pathways in which BPA can stimulate cellular responses at very low doses and where the effects can be U-shaped or inverted U-shaped dose responses, so-called "nonmonotonic" association [15-47].

Increasing numbers of studies in humans showed that a higher concentration of urinary BPA is associated with younger age [7, 14], female sex, non-Hispanic black, low family income [7], low education, and smoking [13, 27]. BPA can leach from polycarbonate plastic food containers and BPA-coated metallic cans. Urinary BPA levels are reported to be associated with food in plastic containers [16], bottled milk feeding [3], and eating canned food [13]. However, urinary BPA levels in the present study were not related to sex, family income, or perceived dietary behavioral risk of BPA exposure. BPA detection, but

Table 5. Literature reporting the association of bisphenol A and obesity in children and adolescents

Authors	Country	Year	N	Age (y)	Method	Limit of detection (ng/mL)	Bisphenol A (ng/mL)	Obesity (%)	Over-weight (%)	Bisphenol A (ng/mL) and obesity	*P*
2011 Carwile JL, et al [24]	USA	2003 - 2006	2,747	18–74	LCMS	0.3	2.05 (median)	33.9		1st Q (BPA ≤1.1) 2nd Q (1.2–2.3) 3rd Q (2.4–4.6) 4th Q (>4.7) OR 1.60-1.85	Significant, 95%CI
2012 Trasande L, et al [25]	USA	2003 - 2008	2838	6–19	LCMS	0.3	2.8 (median)	17.8	34.1	1st Q (BPA ≤1.5) 2nd Q (1.5–2.7) 3rd Q (2.8–5.5) 4th Q (>5.6) OR 2.08–2.57	< 0.001
2012 Bhandari R, et al [26]	USA	2003 - 2008	2200	6–18	LCMS	0.3	4.8	17.7	16.7	1st Q (BPA ≤1.5) 2nd Q (1.5–2.7) 3rd Q (2.8–5.4) 4th Q (>5.4) OR 1.78–2.55	0.002
2012 Wang H, et al [27]	China	2011	259	8–15	LCMS	0.07	0.45 GM	31.7	20.4	Normal BPA 0.33 Obesity BPA 0.57	0.018
2013 Li D, et al [29]	China	2011	1,326	4–12	HPL/FD	0.31	NA		18.3	girl: associated with overweight	Significant, 95%CI
Current study	**Thailand**	**2013 - 2014**	**376**	**3–18**	**LCMS**	**0.05**	**0.68 (median)**	**11.3**	**9.0**	**OR 3.42 (Normal lean vs. obese)**	**0.02**

GM = geometric mean, HPL/FD, HPLC with fluorescence detection, NA = not available, Q = quartile

not its levels, were more significantly associated with children aged 3–6 years than children aged 6–10 years, and adolescents. Our results are consistent with most published studies, which postulate that children consume more food per body weight and are more vulnerable to exposure to products with BPA contamination such as plastic packages and toys [7, 12, 14].

We showed an association between obesity and urinary BPA detection. The BPA detection rate in students with normal weight was significantly higher in the group with BPA <0.05 ng/mL than in the group with BPA >0.05 ng/mL (86.5% vs 77.3%, $P = 0.015$). The BPA detection rate in obese students was significantly higher in the group with BPA >0.05 ng/mL than in the group with BPA <0.05 ng/mL (13.7% vs 4.5%, $P = 0.03$) (**Table 2**). Obesity was significantly associated with BPA detection with an OR of 3.42 (95% CI 1.18–9.95, $P = 0.02$) (**Table 3**). The median BPA levels tended to increase from 0.67 and 0.62 ng/mL in normal weight and overweight children, respectively, to 0.87 ng/mL in obese children, but this trend was not significant (**Table 2**). The median BPA levels adjusted by creatinine tended to increase from 0.51 and 0.31 μg/g Cr in normal weight and overweight children, respectively, to 0.71 μg/g Cr in obese children, but the trend was not significant (**Table 2**). Obesity is a multifactorial and complex disease. Its etiology involves the interaction between genetic factors and environments including endocrine disruptors (EDs). Linking of common EDs, BPA, exposure, and obesity was reported in several human epidemiological studies in adults and children shown in Table 5 [24-27, 29]. All studies showed significant relationships between urinary BPA levels and BMI values or the degree of obesity. Median values or geometric means of BPA widely varied by the age of participants, method for BPA analysis, types of specimens, countries in which studies were conducted, and year of study.

There have been several hypotheses postulated to date for the mechanism of BPA exposure leading to obesity [48]; but the details remain unclear. In vivo studies in mice show that exposure to low doses of BPA during the perinatal development, resulted in increased body weight [49, 50], and BPA was identified as associated with the upregulation of a number of genes in abdominal adipocytes in rats, including those for peroxisome proliferator-activated receptor γ, CCAAT/enhancer-binding protein α, and lipoprotein lipase [51]. In vitro studies showed that BPA acts as a selective estrogen receptor moderator, which can then regulate adipocyte hypertrophy and hyperplasia [52]. BPA was found to stimulate glucocorticoid receptors to promote adipogenesis in preadipocytes (3T3-L1 cell line) [53]. To our knowledge, there is no published study showing increased BPA absorption in obese individuals.

The present cross-sectional study is limited by its small sample size and because sampling was not conducted using a randomized method. A number of questionnaires were not completed, thereby, perhaps affecting the data. This might have been because participants could not understand some of the questions. Therefore, future questionnaires will have to take this into consideration. Urine collection was difficult in small children, particularly from girls. Spot morning urine is not as reliable as 24 hour urine samples or multiple spot urine testing, but it might be acceptable in a larger study. A strength of our study is use of a highly sensitive and standardized LC-MSMS method to analyze urine BPA.

Conclusions

BPA exposure in Thai children and adolescents appears to be lower than that in Northern America, some European, and other Asian countries. Obesity and younger age are significantly associated with BPA detection.

Acknowledgments

We thank the students, families, and teachers for participating in this study and the pediatric residents and pediatric endocrinology fellows for helping with the collection of data and urine specimens. We also thank Miss Nuanpan Siripen for her kind help and expertise in analyzing urine creatinine. This study was supported by a Thailand Research grant (MRG5580203) and Ratchadapiseksompotch Funds (RA56/021) and of the Faculty of Medicine, Chulalongkorn University.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). Reprod Toxicol. 2007; 24:139-77.
2. Braun JM, Kalkbrenner AE, Calafat AM, Baneft JT,

Ye X, Silva MJ, et al. Variability and predictors of urinary bisphenol A concentrations during pregnancy. Environ Health Perspect. 2011; 119:131-7.
3. Rhie YJ, Nam HK, Oh YJ, Kim HS, Lee KH. Influence of bottle-feeding on serum bisphenol A levels in infants. J Korean Med Sci. 2014; 29:261-4.
4. Olea N, Pulgar R, Perez P, Olea-Serrano F, Rivas A, Novillo-Fertrell A, et al. Estrogenicity of resin-based composites and sealants used in dentistry. Environ Health Perspect. 1996; 104:298-305.
5. Duty SM, Mendonca K, Hauser R, Calafat AM, Ye X, Meeker JD, et al. Potential sources of bisphenol A in the neonatal intensive care unit. Pediatrics. 2013; 131: 483-9.
6. Silver MK, O'Neill MS, Sowers MR, Park SK. Urinary bisphenol A and type-2 diabetes in U.S. adults: data from NHANES 2003–2008. PloS One. 2011; 6:e26868.
7. Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. Environ Health Perspect. 2008; 116:39-44.
8. Bushnik T, Haines D, Levallois P, Levesque J, van Oostdam J, Viau C. Lead and bisphenol A concentrations in the Canadian population. Health Rep. 2010; 21:7-18.
9. Pirard C, Sagot C, Deville M, Dubois N, Charlier C. Urinary levels of bisphenol A, triclosan and 4-nonylphenol in a general Belgian population. Environ Int. 2012; 48:78-83.
10. Frederiksen H, Nielsen JK, Morck TA, Hansen PW, Jensen JF, Nielsen O, et al. Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban Danish mother-child pairs. Int J Hyg Environ Health. 2013; 216:772-83.
11. Frederiksen H, Aksglaede L, Sorensen K, Nielsen O, Main KM, Skakkebaek NE, et al. Bisphenol A and other phenols in urine from Danish children and adolescents analyzed by isotope diluted TurboFlow-LC-MSMS. Int J Hyg Environ Health. 2013; 216: 710-20.
12. Becker K, Goen T, Seiwert M, Conrad A, Pick-Fuss H, Muller J, et al. GerES IV: phthalate metabolites and bisphenol A in urine of German children. Int J Hyg Environ Health. 2009; 212:685-92.
13. Casas M, Valvi D, Luque N, Ballesteros-Gomez A, Carsin AE, Fernandez MF, et al. Dietary and sociodemographic determinants of bisphenol A urine concentrations in pregnant women and children. Environ Int. 2013; 56:10-8.
14. Zhang Z, Alomirah H, Cho HS, Li YF, Liao C, Minh TB, et al. Urinary bisphenol A concentrations and their implications for human exposure in several Asian countries. Environ Sci Techno1. 2011; 45: 7044-50.
15. Ha M, Kwon HJ, Leem JH, Kim HC, Lee KJ, Park I, et al. Korean Environmental Health Survey in Children and Adolescents (KorEHS-C): survey design and pilot study results on selected exposure biomarkers. Int J Hyg Environ Health. 2014; 217:260-70.
16. Nahar MS, Soliman AS, Colacino JA, Calafat AM, Battige K, Hablas A, et al. Urinary bisphenol A concentrations in girls from rural and urban Egypt: a pilot study. Environ Health. 2012; 11:20.
17. Heffeman AL, Aylward LL, Toms LM, Eaglesham G, Hobson P, Sly PD, et al. Age related trends in urinary excretion of bisphenol A in Australian children and adults: evidence from a pooled sample study using samples of convenience. J Toxicol Environ Health. Part A. 2013; 76:1039-55.
18. Sriphrapradang C, Chailurkit LO, Aekplakorn W, Ongphphadhanakul B. Association between bisphenol A and abnormal free thyroxine level in men. Endocrine. 2013; 44:441-7.
19. Alonso-Magdalena P, Laribi O, Ropero AB, Fuentes E, Ripoll C, Soria B, et al. Low doses of bisphenol A and diethylstilbestrol impair Ca^{2+} signals in pancreatic α-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. Environ Health Perspect. 2005; 113:969-77.
20. Batista TM, Alonso-Magdalena P, Vieira E, Amaral ME, Cederroth CR, Nef S, et al. Short-term treatment with bisphenol-A leads to metabolic abnormalities in adult male mice. PloS One. 2012; 7:e33814.
21. Alonso-Magdalena P, Morimoto S, Ripoll C, Fuentes E, Nadal A. The estrogenic effect of bisphenol A disrupts pancreatic β-cell function *in vivo* and induces insulin resistance. Environ Health Perspect. 2005; 114: 106-12.
22. Shankar A, Teppala S. Relationship between urinary bisphenol A levels and diabetes mellitus. J Clin Endocrinol Metab. 2011; 96:3822-6.
23. Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA. 2008; 300:1303-10.
24. Carwile JL, Michels KB. Urinary bisphenol A and obesity: NHANES 2003–2006. Environ Res. 2011; 111: 825-30.
25. Trasande L, Attina TM, Blustein J. Association

between urinary bisphenol A concentration and obesity prevalence in children and adolescents. JAMA. 2012; 308:1113-21.
26. Bhandari R, Xiao J, Shankar A. Urinary bisphenol A and obesity in U.S. children. Am J Epidemiol. 2013; 177:1263-70.
27. Wang HX, Zhou Y, Tang CX, Wu JG, Chen Y, Jiang QW. Association between bisphenol A exposure and body mass index in Chinese school children: a cross-sectional study. Environ Health. 2012; 11:79.
28. Shankar A, Teppala S, Sabanayagam C. Urinary bisphenol-A levels and measures of obesity: results from the National Health and Nutrition Examination Survey 2003–2008. ISRN. Endocrinol. 2012; 965:243.
29. Li DK, Miao M, Zhou Z, Wu C, Shi H, Liu X, et al. Urine bisphenol-A level in relation to obesity and overweight in school-age children. PloS One. 2013; 8: e65399.
30. Eng DS, Lee JM, Gebremariam A, Meeker JD, Peterson K, Padmanabhan V. Bisphenol A and chronic disease risk factors in US children. Pediatrics. 2013; 132: e637-45.
31. Melzer D, Rice NE, Lewis C, Henley WE, Galloway TS. Association of urinary bisphenol A concentration with heart disease: evidence from NHANES 2003/06. PloS One. 2010; 5:e8673.
32. Melzer D, Gates P, Osborn NJ, Henley WE, Cipelli R, Young A, et al. Urinary bisphenol A concentration and angiography-defined coronary artery stenosis. PloS One. 2012; 7:e43378.
33. Meeker JD, Calafat AM, Hauser R. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. Environ Sci Techno1. 2010; 44:1458-63.
34. Braun JM, Kalkbrenner AE, Calafat AM, Yolton K, Ye X, Dietrich KN, et al. Impact of early-life bisphenol a exposure on behavior and executive function in children. Pediatrics. 2011; 128:873-82.
35. Harley KG, Gunier RB, Kogut K, Johnson C, Bradman A, Calafat AM, et al. Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children. Environ Res. 2013; 126:43-50.
36. Iamopas O, Chongviriyaphan N, Suthutvoravut U. Metabolic syndrome in obese Thai children and adolescents. J Med Assoc Thai. 2011; 94:126-32.
37. Mo-suwan L, Tongkumchum P, Puetpaiboon A. Determinants of overweight tracking from childhood to adolescence: a 5 y follow-up study of Hat Yai schoolchildren. Int J Obes Relat Metab Disord. 2000; 12:1642-7.
38. Aekplakorn W, Mo-Suwan L. Prevalence of obesity in Thailand. Obes Rev. 2009; 10:589-92.
39. Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. J Clin Endocrinol Metab. 2008; 93(11 Suppl. 1):S9-30.
40. Volkel W, Colnot T, Csanady GA, Filser JG, Dekant W. Metabolism and kinetics of bisphenol A in humans at low doses following oral administration. Chem Res Toxicol. 2002; 15:1281-7.
41. Stahlhut RW, Welshons WV, Swan SH. Bisphenol A data in NHANES suggest longer than expected half life, substantial nonfood exposure, or both. Environ Health Perspect. 2009; 117:784-9.
42. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, et al. Centers for Disease Control and Prevention 2000 Growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics. 2002; 109:45-60.
43. Nepomnaschy PA, Baird DD, Weinberg CR, Hoppin JA, Longnecker MP, Wilcox AJ. Within-person variability in urinary bisphenol a concentrations: measurements specimens after long-term frozen storage. Environ Res. 2009; 109:734-7.
44. Valentin J. Basic anatomical and physiological data for use in radiological protection: reference values. A report of age- and gender-related differences in the anatomical and physiological characteristics of reference individuals. ICRP Publication 89. Ann ICRP. 2002; 32:1–277.
45. Vandenberg LN, Maffini MV, Sonnenschein C, Rubin BS, Soto AM. Bisphenol-A and the great divide: a review of controversies in the field of endocrine disruption. Endocrine Rev. 2009; 30:75-95.
46. Wozniak AL, Bulayeva NN, Watson CS. Xenoestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-α-mediated Ca^{2+} fluxes and prolactin release in GH3/B6 pituitary tumor cells. Environ Health Perspect. 2005; 113:431-9.
47. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocrine Rev. 2012; 33:378-455.
48. Vom Saal FS, Nagel SC, Coe BL, Angle BM, Taylor JA. The estrogenic endocrine disrupting chemical bisphenol A (BPA) and obesity. Mol Cell Endocrinol. 2012; 354;74-84.
49. Miyawaki J, Sakayama K, Kato H, Yamamoto H, Masuno H. Perinatal and postnatal exposure to bisphenol A increases adipose tissue mass and serum

cholesterol level in mice. J Atheroscler Thromb. 2007; 14:245-52.
50. Newbold RR, Padilla-Banks E, Snyder RJ, Phillips TM, Jefferson WN. Developmental exposure to endocrine disruptors and the obesity epidemic. Reprod Toxicol. 2007; 23:290-6.
51. Somm E, Schwitzgebel VM, Toulotte A, Cederroth CR, Combescure C, Nef S, et al. Perinatal exposure to bisphenol A alters early adipogenesis in the rat. Environ Health Perspect. 2009; 117:1549-55.
52. Grun F, Blurnberg B. Endocrine disrupters as obesogens. Mol Cell Endocrinol. 2009; 304;19-29.
53. Sargis RM, Johnson DN, Choudhury RA, Brady MJ. Environmental endocrine disruptors promote adipogenesis in the 3T3-L1 cell line through glucocorticoid receptor activation. Obesity. 2010; 18: 1283-8.