THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
Journal of Child Psychology and Psychiatry 54:8 (2013), pp 890–899 doi:10.1111/jcpp.12050

Bisphenol A in relation to behavior and learning of school-age children

Soon-Beom Hong,[1,*] Yun-Chul Hong,[2,*] Jae-Won Kim,[1] Eun-Jin Park,[3] Min-Sup Shin,[1] Boong-Nyun Kim,[1] Hee-Jeong Yoo,[1] In-Hee Cho,[4] Soo-Young Bhang,[5] and Soo-Churl Cho[1]

[1]Division of Child and Adolescent Psychiatry, Department of Psychiatry, Seoul National University College of Medicine, Seoul; [2]Department of Preventive Medicine, Seoul National University College of Medicine and Institute of Environmental Medicine, Seoul; [3]Department of Psychiatry, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea; [4]Department of Psychiatry, Gil Medical Center, Gachon University of Medicine and Science, Incheon; [5]Department of Psychiatry, Gangnam Eulji Hospital, Eulji University, Seoul, Korea

Background: Bisphenol A (BPA) has been shown to affect brain and behavior in rodents and nonhuman primates, but there are few studies focusing on its relationship to human neurobehavior. We aimed to investigate the relationship between environmental exposure to BPA and childhood neurobehavior. **Methods:** Urinary BPA concentrations and behavioral and learning characteristics were assessed in a general population of 1,089 children, aged 8–11 years. The main outcome measures were the Child Behavior Checklist (CBCL) and the Learning Disability Evaluation Scale (LDES). **Results:** Urinary levels of BPA were positively associated with the CBCL total problems score and negatively associated with the learning quotient from the LDES. The linear association with the CBCL anxiety/depression score and the quadratic association with the LDES listening score were significant after correction for multiple comparisons. **Conclusions:** Environmental exposure to BPA might be associated with childhood behavioral and learning development. The results suggest possible nonmonotonic relationships. **Keywords:** Bisphenol A, child behavior, child learning, nonmonotonic dose–response.

Bisphenol A (BPA) is a widespread industrial chemical. It is commonly used to synthesize polycarbonate plastics and epoxy resins, and these plastic polymers are extensively applied to the manufacture of various articles of daily use, including, for example, plastic food storage containers, polycarbonate beverage bottles, epoxy-lined food cans, baby formula bottles, and dental sealants, to name a few (Lakind & Naiman, 2011; Roy, Chakraborty & Chakraborty, 2009); thus increasing concerns have been raised over the past decade about the impact of environmental BPA on human health.

Based on the chemical nature of BPA, an estrogenic compound, concerns have been directed largely toward its endocrine or sexual/reproductive consequences. On the other hand, estrogen also plays an important role in brain development (Panzica et al., 2007), on which ground BPA was hypothesized and indeed found to affect certain neural circuits and subsequent behaviors, mainly in rats and mice (Laviola, Gioiosa, Adriani & Palanza, 2005; Leranth, Szigeti-Buck, Maclusky & Hajszan, 2008; Palanza, Gioiosa, vom Saal & Parmigiani, 2008; Xu, Zhang, Wang, Ye & Luo, 2010). However, even though BPA has further been suggested to act on several endocrine and neural pathways, and given that BPA is generally accepted to be detected in most people living in developed countries (i.e., BPA was detected in 92.6% and 99% of urine samples from the US and German general population, respectively) (Becker et al., 2009; Calafat, Ye, Wong, Reidy & Needham, 2008), with daily BPA intakes likely to be highest in children (Lakind & Naiman, 2011), human studies of environmentally relevant, low-dose exposure to BPA in relation to neurobehavior are surprisingly lacking in numbers.

In humans, one previous study (Braun et al., 2009) has measured maternal BPA levels during pregnancy and later addressed the behavioral relevance on their children at 2 years of age; the authors have suggested an association between prenatal BPA exposure and externalizing behaviors of female children. A more recent study also using urine samples from pregnant women investigated BPA concentrations in relation to possible social impairment in their children between the ages 7 and 9 years (Miodovnik et al., 2011). Later on, Braun et al. (2011) identified that the impact of prenatal BPA exposure remained at 3 years of age, and that it was still modified by child gender (Braun et al., 2011).

In this landmark follow-up study, the investigators added BPA measurements from childhood urine samples (1, 2, and 3 years of age), and found that gestational rather than childhood BPA exposure had greater impact on neurobehavior. Similarly, Perera et al. (2012) also collected urine samples both from the mothers during pregnancy and later from their children (3 and 4 years of age), and reported that higher prenatal BPA exposure was associated with more severe behavioral and emotional problems in boys (Perera et al., 2012). However, apart from the replicated finding that prenatal period may be a more sensitive window for the neurobehavioral impact of

*These authors contributed equally to this work.
Conflict of interest statement: No conflicts declared.

BPA exposure, another interesting finding was noted regarding the postnatal urinary BPA concentration: it showed a significant negative association with one of the CBCL syndrome scores (Perera et al., 2012).

Although the limited number of studies in the literature about the impact of BPA on human neurobehavior has so far focused on prenatal exposure to this compound, little is known about its relationship with childhood neurobehavior, especially regarding later BPA exposure beyond the age addressed in the aforementioned studies. Thus, we aimed to investigate the association between urinary concentrations of BPA and measures of cognitive and behavioral characteristics in a general population of school-age children.

Methods

Participants were recruited from five different administrative regions in Korea, among which Seoul and Seongnam are urban cities, Incheon and Ulsan are industrial cities, and Yeoncheon is a rural district. We selected from each city two or three schools that represented well the local demographics, and sent letters of invitation to participate in our study addressed to parents of children studying at third or fourth grade (age range 8–11). Detailed information about the study was given to parents and children, and then written informed consent was obtained before the study entry. The study protocol was approved by the institutional review board of the Seoul National University Hospital.

Assessment of the child's behavior and learning

Child Behavior Checklist, parent-rated. Emotional and behavioral problems of the children were assessed by their parents using the Korean version of the Child Behavior Checklist (CBCL) (Achenbach, 1991). The CBCL is an age- and sex-standardized questionnaire composed of 108 items rated on a three-step response scale ranging from 0 (absent) to 2 (very often present). Eight narrow band subscales for specific areas of functioning (social withdrawal, somatic complaints, anxiety/depression, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior) and three broad band subscales for overall problems (internalizing, externalizing, and total problems) are empirically derived; the sum of individual item scores are converted to T-scores, in which higher scores indicate more severe problems. The CBCL is one of the best-studied and widely translated instruments for the evaluation of child and adolescent psychopathology; the Korean version was also standardized (Oh & Lee, 1990) and has been broadly used in many fields.

Learning Disability Evaluation Scale, parent-rated. The Learning Disability Evaluation Scale (LDES) (McCarney, 1996) consists of 88 items describing the observed characteristics of students with a learning disability. Each item score is rated on a 3-point scale ranging from 1 (rarely or never) to 3 (all or most of the time), and the items are factor analyzed and clustered into seven different subscales of listening, thinking, speaking, reading, writing, spelling, and mathematical calculations; the sum of individual item scores is converted to age-adjusted standard scores, in which higher scores indicate better performance. In addition, as a global measure of learning disabilities, the learning quotient (LQ) is converted from the sum of seven subscales' standard scores. The Korean version was age-standardized among children, and found to be a valid and reliable instrument for screening specific learning disorders (Shin, Hong, Kim & Cho, 1998).

Assessment of the child's IQ and possible risk factors regarding the child's neurobehavior

Each child was individually administered the abbreviated form of the Korean Educational Development Institute's Wechsler Intelligence Scales for Children (KEDI-WISC) (Park, Yoon, Park, Park & Kwon, 1996), not only to assess their overall cognitive strengths and weaknesses but also to use their intelligence quotient (IQ) as a covariate in analyzing the data. Scores from the abbreviated battery are known to highly correlate with the WISC full scale IQ, both in the widely translated original instrument, the revised version of the WISC (Kaufman, 1976), and in the age-standardized Korean version, KEDI-WISC (Kim & Kim, 1986).

Parents completed a questionnaire about demographic and other possibly relevant data, including maternal and paternal education, socioeconomic status, maternal age at the child's birth, child's gestational age and weight at birth, as well as family history of psychiatric disorders (collected through open-ended questions).

Measurement of urinary BPA concentration

Urine was collected from each child between 9:00 and 11:00 a.m. at school. Immediately after collection, samples were stored at −20 °C until analysis. Later, urinary concentrations of BPA were measured using the methods described by Matsumoto and colleagues (Matsumoto et al., 2003), with minor modifications. In brief, for the analysis of total urinary BPA (conjugated and free forms), 30 μl of 2.0 M sodium acetate (pH 5.0) and 20 μl of β-glucuronidase (Roche, Mannheim, Germany) were added to 1 ml aliquots of each urine sample. The reaction mixture was incubated at 37 °C for 16 hr. Then, we added 100 μl of 2 N HCl and extracted the mixture with 3 ml of ethyl acetate that contained 50 μl of 100 μg/l $^{13}C_{12}$-BPA in acetonitrile as an internal standard. After the extraction, we trans-

ferred 2 ml of supernatant to a new glass tube and evaporated the solution. The residue was dissolved with 300 μl of 60% acetonitrile, and 5 μl of the resultant was injected into our high performance liquid chromatography-electron spray ionization tandem mass spectrometry (HPLC-ESI-MS/MS) apparatus (Agilent 6410A; Santa Clara, CA, USA). The limit of detection (LOD) was 0.15 μg/l.

Blood levels of lead as well as urinary levels of phthalate metabolites (mono-n-butyl phthalate, MnBP; mono-2-ethyl-5-oxohexyl phthalate, MEOHP; mono-2-ethylhexyl phthalate, MEHP) and cotinine were also measured using the methods described elsewhere (Cho et al., 2010; Kim, Cho, et al., 2009; Kim, Kim, et al., 2009).

Statistical analyses

Differences between the children included in and excluded from the main analyses were estimated using Student's *t*-tests for continuous variables and chi-square tests for categorical variables. Urinary BPA concentration (μg/l) was standardized with creatinine (Cr) level (g/l) to control for individual differences in urine dilution (Ye, Wong, Bishop & Calafat, 2011); the resultant BPA concentrations (μg/g Cr) followed a log-normal distribution and were, therefore, log10-transformed for the statistical analysis.

We performed multiple linear regression analyses (ordinary least squares) using the log10-transformed, Cr-standardized, urinary BPA concentration as the primary independent variable, and adjusting for numerous potential confounders including demographic and obstetric variables, psychiatric family histories, and biological levels of environmental toxicants other than BPA. The regression equation was also estimated including an interaction term between urinary BPA concentration and gender, or a quadratic term for urinary BPA concentration. All statistical analyses were performed using STATA 11.0 (STATA Corp., College Station, TX). All results were considered to be statistically significant when *p*-value was less than 0.05.

Results

A total of 1,089 children were recruited. The participation rates were 62.2%, 65.3%, and 63.3% in urban, industrial, and rural regions, respectively. The mean age was 9.05 ± 0.70 years (range 8–11), and 571 (52.4%) were male and 518 (47.6%) were female. Of those, urinary BPA data were available for 1,012 children, and the other 77 who refused to provide urine samples were excluded from the study. An additional four were further excluded from the main analyses, because two had a history of seizure disorder, one of neonatal hypoxia, and one of head trauma accompanied by cerebral hemorrhage. The characteristics of the 1,008 participants are described in Table 1. In addition, the similarities and differences between the children included in and excluded from the study are shown in Table S1 (online supporting information). For those included in the main analyses, male and female participants were further compared as in Table S1.

Estimated daily BPA intake

In this study, no measurement of urinary BPA before being standardized with Cr level was below the LOD, and the lowest nonstandardized BPA value was 0.16 μg/l. The minimum, 25th percentile, median, 75th percentile, and maximum of urinary BPA concentration were 0.16 μg/l, 0.67 μg/l, 1.23 μg/l, 2.29 μg/l, and 125.16 μg/l for nonstandardized BPA; and 0.14 μg/g Cr, 0.76 μg/g Cr, 1.28 μg/g Cr, 2.18 μg/g Cr, and 300.15 μg/g Cr for Cr-standardized BPA, respectively. By applying the equation used by Lakind and Naiman (Lakind & Naiman, 2011), and by adopting the same 24-hr urinary output data (700 ml/day for 10-year olds), we have estimated the mean daily BPA intake of our children as 47.16 ng/kg.

Association with behavioral and learning problems

Urinary concentrations of BPA were positively associated with the CBCL total problems score (B = 0.85;

Table 1 Demographic characteristics of the subjects

Characteristics	N = 1,008
Demographic variables	
Age (years): *M* (*SD*)	9.05 (0.70)
Gender (female, %)	47.32
Region, urban (%)	43.45
Region, industrial (%)	39.48
Region, rural (%)	17.07
Paternal education (years): *M* (*SD*)	13.75 (2.13)
Yearly income >$25,000 (%)	61.45
Child's IQ: *M* (*SD*)	110.07 (14.41)
Obstetric variables	
Maternal age at pregnancy (years): *M* (*SD*)	28.50 (3.75)
Gestational age at birth (weeks): *M* (*SD*)	39.74 (1.28)
Child's birth weight (kg): *M* (*SD*)	3.23 (0.45)
Psychiatric family histories	
ADHD (%)	1.48
Mental retardation (%)	1.28
Depressive disorder (%)	4.16
Bipolar disorder (%)	0.39
Anxiety disorder (%)	0.89
Biological levels of toxicants	
Lead (μg/dl): geometric mean (GSD)	1.80 (1.40)
MnBP (μg/g Cr): geometric mean (GSD)	51.80 (1.86)
MEOHP + MEHP (μg/g Cr): geometric mean (GSD)	44.63 (1.95)
Cotinine (ng/ml): geometric mean (GSD)	1.83 (3.57)
Bisphenol A (μg/g Cr): geometric mean (GSD)	1.32 (2.32)

The variables detailed above were adjusted for as covariates in the following main analyses.
ADHD, attention-deficit/hyperactivity disorder; Cr, creatinine; GSD, geometric standard deviation; IQ, intelligence quotient; MEHP, mono-2-ethylhexyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MnBP, mono-n-butyl phthalate; SD, standard deviation.

$p = 0.00$; 95% CI 0.26–1.44; adjusted $R^2 = 0.02$) and negatively associated with the LQ from the LDES ($B = -1.90$; $p = 0.02$; 95% CI −3.50 to −0.30; adjusted $R^2 = 0.20$); these associations were significant when adjusting for demographic variables (i.e., age, gender, region, paternal education, and yearly income) and child's IQ. We have further analyzed with each of the subscale scores from the CBCL and LDES as the dependent variable. Urinary concentrations of BPA were positively associated with the CBCL scores of anxiety/depression ($B = 1.07$; $p = 0.00$; 95% CI 0.57–1.58; adjusted $R^2 = 0.00$), social problems ($B = 1.22$; $p = 0.01$; 95% CI 0.34–2.11; adjusted $R^2 = 0.03$), attention problems ($B = 0.93$; $p = 0.00$; 95% CI 0.32–1.53; adjusted $R^2 = 0.05$), and internalizing problems ($B = 0.66$; $p = 0.01$; 95% CI 0.16–1.16; adjusted $R^2 = 0.00$), and negatively associated with the LDES scores of thinking ($B = -0.36$; $p = 0.03$; 95% CI −0.70 to −0.02; adjusted $R^2 = 0.14$), reading ($B = -0.41$; $p = 0.04$; 95% CI −0.81 to −0.00; adjusted $R^2 = 0.18$), writing ($B = -0.31$; $p = 0.01$; 95% CI −0.55 to −0.07; adjusted $R^2 = 0.16$), and mathematical calculations ($B = -0.43$; $p = 0.00$; 95% CI −0.73 to −0.12; adjusted $R^2 = 0.18$); these associations were significant when adjusting for demographic variables and child's IQ. Among these results, the association with the CBCL anxiety/depression score was significant after the Bonferroni correction for a total of 19 multiple comparisons (p-value less than 0.05/19 = 0.00263). However, adjustment for multiple comparisons might not have been necessary, and p-values falling between the Bonferroni ($p = 0.00263$) and traditional ($p = 0.05$) significance thresholds should not be dismissed (Rothman, 1990). Also of note is that even for those associations which failed to attain statistical significance, they were all in hypothesized directions as well (Table 2).

We have also performed weighting adjustments to compensate for the differences between the included and excluded groups of children. By running a logistic regression with a dummy indicating either included or excluded as the dichotomous dependent variable and characteristics that turned out to be different between the two groups as independent variables, we identified the predicted probability of study inclusion for each observation. We then adjusted each observation by weighting with the inverse of this predicted probability (Kessler et al., 2004). Similar results were obtained with the weighting adjustments (Table S2).

An alternative method of controlling for urine dilution is to include creatinine in the regression model as a covariate (Barr et al., 2005): using this approach, the list of significant associations did not substantially change (data not shown; available upon request). No significant association was found between urinary concentrations of BPA and the KEDI-WISC scores of vocabulary, arithmetic, picture arrangement, block design, as well as the VIQ, PIQ, and the FSIQ of the children (data not shown; available upon request).

Table 2 Adjusted associations between urinary bisphenol A concentration and the scores from the CBCL and LDES

$N = 1{,}008$	B (SE)	p	95% CI
CBCL			
Social withdrawal	1.02 (0.79)	0.22	−0.70, 2.75
Somatic complaints	0.13 (0.35)	0.70	−0.62, 0.89
Anxiety/depression	1.07 (0.23)	**0.00**	0.57, 1.58
Social problems	1.22 (0.40)	0.01	0.34, 2.11
Thought problems	0.37 (0.25)	0.17	−0.18, 0.92
Attention problems	0.93 (0.27)	0.00	0.32, 1.53
Delinquent behavior	0.33 (0.22)	0.15	−0.14, 0.81
Aggressive behavior	0.38 (0.32)	0.25	−0.32, 1.10
Internalizing problems	0.66 (0.22)	0.01	0.16, 1.16
Externalizing problems	0.38 (0.29)	0.21	−0.25, 1.02
Total problems	0.85 (0.27)	0.00	0.26, 1.44
LDES			
Listening	−0.44 (0.22)	0.07	−0.92, 0.04
Thinking	−0.36 (0.15)	0.03	−0.70, −0.02
Speaking	−0.30 (0.15)	0.06	−0.63, 0.01
Reading	−0.41 (0.18)	0.04	−0.81, −0.00
Writing	−0.31 (0.10)	0.01	−0.55, −0.07
Spelling	−0.29 (0.14)	0.06	−0.61, 0.01
Calculations	−0.43 (0.13)	0.00	−0.73, −0.12
Learning quotient	−1.90 (0.73)	0.02	−3.50, −0.30

The analyses were adjusted for age, gender, region, paternal education, yearly income, and child's IQ.
Log10-transformed, creatinine-standardized values were used for urinary bisphenol A concentration.
Higher scores on the CBCL indicate greater problems, and on the LDES better performance.
p-values significant after correction for the number of dependent variables tested ($p < 0.05/19 = 0.00263$) were boldtyped.
p-values for F statistics were below 0.05, except for the CBCL thought problems score.
B, unstandardized regression coefficient; CI, confidence interval; CBCL, child behavior checklist; LDES, learning disability evaluation scale; SE, standard error.

Assessment of sexually dimorphic association

Including an interaction term (urinary BPA concentration x gender) in the regression equation revealed that the effect of urinary BPA concentration on our dependent variables was not significantly modified by gender. In fact, not a single effect modification by sex reached a p-value below 0.10. To further clarify this finding, we have performed the multiple linear regression analyses separately for male and female children, and presented the results in Table S3.

Assessment of nonlinear association

The quadratic term for urinary BPA level was negatively associated with the CBCL scores of delinquent behavior ($B = -0.95$; $p = 0.00$; 95% CI −1.61 to −0.29; adjusted $R^2 = 0.01$) and externalizing problems ($B = -0.62$; $p = 0.02$; 95% CI −1.15 to −0.09; adjusted $R^2 = 0.01$), and positively associated with the LDES listening score ($B = 0.64$; $p = 0.00$; 95% CI 0.37–0.90; adjusted $R^2 = 0.11$); these associations

were significant when adjusting for demographic variables and child's IQ (Table 3). Among these results, the nonlinear association with the LDES listening score was significant after correction for 19 multiple comparisons (p-value less than 0.05/19 = 0.00263). The significant quadratic association found between urinary concentration of BPA and the LDES listening score is illustrated graphically in Figure 1. Again, the results were similar either with or without the weighting adjustments (Table S4). The vertices of the significant quadratic functions (parabolas) described above were located at urinary BPA concentrations of 2.56, 3.70, and 4.02 μg/g Cr, respectively, meaning that a nonlinear association between exposure and outcome might actually be present within the range of low-dose BPA exposures. To provide an alternative perspective, we have also presented the mean CBCL and LDES scores by quartiles of urinary BPA concentration (Table 4 and Figure S1).

We have checked the nonlinear associations separately for male and female children, and found that nonlinear associations with the CBCL scores of delinquent behavior ($B = -1.61$; $p = 0.00$; 95% CI −2.53 to −0.70; adjusted $R^2 = 0.05$), aggressive behavior ($B = -1.56$; $p = 0.00$; 95% CI −2.38 to −0.74; adjusted $R^2 = 0.01$), and externalizing problems ($B = -1.69$; $p = 0.00$; 95% CI −2.50 to −0.88; adjusted $R^2 = 0.02$) were significant after correction for 19 multiple comparisons in male children (Table S5).

Table 3 Quadratic associations between urinary bisphenol A concentration and the scores from the CBCL and LDES

N = 1,008	B (SE)	p	95% CI
CBCL			
Social withdrawal			
BPA	1.35 (0.92)	0.16	−0.66, 3.36
BPA^2	−0.60 (1.11)	0.59	−3.02, 1.81
Somatic complaints			
BPA	0.21 (0.49)	0.67	−0.87, 1.30
BPA^2	−0.15 (0.45)	0.74	−1.14, 0.83
Anxiety/depression			
BPA	1.10 (0.28)	**0.00**	0.49, 1.71
BPA^2	−0.04 (0.34)	0.89	−0.79, 0.70
Social problems			
BPA	1.30 (0.50)	0.02	0.19, 2.41
BPA^2	−0.14 (0.45)	0.75	−1.13, 0.84
Thought problems			
BPA	0.26 (0.28)	0.36	−0.34, 0.87
BPA^2	0.19 (0.27)	0.48	−0.39, 0.78
Attention problems			
BPA	0.93 (0.28)	0.00	0.32, 1.54
BPA^2	−0.00 (0.28)	0.98	−0.63, 0.62
Delinquent behavior			
BPA	0.85 (0.24)	0.00	0.32, 1.37
BPA^2	−0.95 (0.30)	0.00	−1.61, −0.29
Aggressive behavior			
BPA	0.68 (0.28)	0.03	0.05, 1.30
BPA^2	−0.54 (0.28)	0.08	−1.16, 0.08
Internalizing problems			
BPA	0.58 (0.28)	0.05	−0.02, 1.20
BPA^2	0.13 (0.34)	0.69	−0.60, 0.88
Externalizing problems			
BPA	0.72 (0.23)	0.01	0.20, 1.24
BPA^2	−0.62 (0.24)	0.02	−1.15, −0.09
Total problems			
BPA	0.94 (0.23)	0.00	0.42, 1.45
BPA^2	−0.16 (0.32)	0.63	−0.86, 0.54
LDES			
Listening			
BPA	−0.81 (0.21)	**0.00**	−1.27, −0.34
BPA^2	0.64 (0.12)	**0.00**	0.37, 0.90
Thinking			
BPA	−0.48 (0.14)	0.00	−0.79, −0.17
BPA^2	0.21 (0.14)	0.16	−0.10, 0.52
Speaking			
BPA	−0.45 (0.17)	0.01	−0.82, −0.08
BPA^2	0.25 (0.23)	0.29	−0.25, 0.77
Reading			
BPA	−0.56 (0.19)	0.01	−0.99, −0.14
BPA^2	0.27 (0.16)	0.11	−0.07, 0.62
Writing			
BPA	−0.38 (0.12)	0.00	−0.65, −0.11
BPA^2	0.12 (0.13)	0.36	−0.16, 0.41
Spelling			
BPA	−0.48 (0.18)	0.02	−0.88, −0.08
BPA^2	0.32 (0.17)	0.09	−0.06, 0.72
Calculations			
BPA	−0.40 (0.14)	0.01	−0.70, −0.09
BPA^2	−0.05 (0.16)	0.74	−0.41, 0.30
Learning quotient			
BPA	−2.69 (0.69)	**0.00**	−4.21, −1.17
BPA^2	1.37 (0.65)	0.05	−0.04, 2.79

The analyses were adjusted for age, gender, region, paternal education, yearly income, and child's IQ.
Log10-transformed, creatinine-standardized values were used for urinary bisphenol A concentration.
Higher scores on the CBCL indicate greater problems, and on the LDES better performance.
p-values significant after correction for the number of dependent variables tested ($p < 0.05/19 = 0.00263$) were bold-typed.
p-values for F statistics were below 0.05, except for the CBCL thought problems score.
B, unstandardized regression coefficient; CI, confidence interval; CBCL, child behavior checklist; LDES, learning disability evaluation scale; SE, standard error.

Additional analyses regarding the selection of confounders

We have further incorporated four additional models adjusting for different potential confounders. History of obstetric adversities and family history of mental disorders are known to be associated with many psychiatric conditions, and thus might reflect a general susceptibility of the brain, increasing the vulnerability to BPA exposure. Biological levels of other toxicants might also confound the effects of BPA, especially if people are usually coexposed to them from the environment. However, these issues have not been clearly investigated regarding BPA. To confirm whether the results are consistent when

some of these potential confounders are adjusted or not, we have further conducted supplementary analyses at different levels of covariates. The results were similar when adjusting for demographic and obstetric variables, psychiatric family histories, and biological levels of environmental toxicants other than BPA (Tables S6 and S7). See Table 1 for the details of these covariates.

To examine a potential collinearity problem, we looked at whether urinary level of BPA was correlated with levels of other environmental toxicants and found that only the MnBP level had a significant positive association ($p = 0.02$). We also checked the variance inflation factor (VIF) among variables and found that no VIF was greater than 4.42.

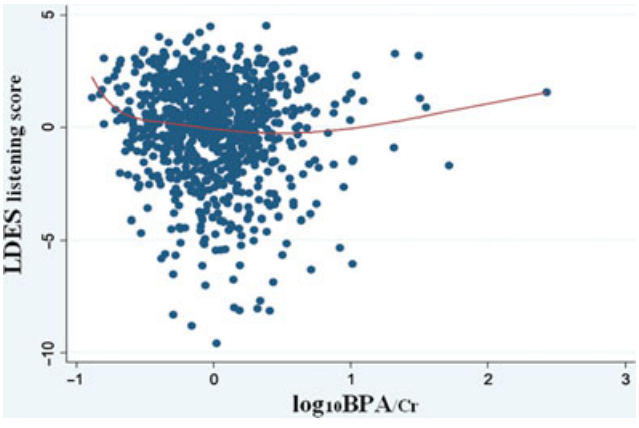

Figure 1 Regression spline smoother with partial scatter plot illustrating the relationship between urinary bisphenol A concentration and the LDES listening score. BPA, bisphenol A; Cr, creatinine; LDES, learning disability evaluation scale

Discussion

Our findings suggest that urinary BPA concentration might be associated with multiple features of childhood neurobehavior, possibly contributing to maladaptive behavior and problematic learning in school-age children. This is in line with the results from many previous animal studies. Prenatal or neonatal exposure to BPA in mice or rats was found to induce impairments in spatial learning and passive avoidance memory (Xu et al., 2010); reduce D-amphetamine-related reinforcing effect, which may imply reduced ability to learn from positive reinforcements (Laviola et al., 2005); trigger learned helplessness behavior in response to electrical shock, a possible sign of both depression and impaired learning (Negishi et al., 2004); bring about depression-like behavior, as shown by struggling less in the forced swimming test (Fujimoto, Kubo & Aou, 2006); stimulate motor hyperactivity (Ishido, Masuo, Kunimoto, Oka & Morita, 2004) and aggressiveness (Kawai et al., 2003); alter play behavior, especially in terms of sociosexual exploration (Dessi-Fulgheri, Porrini & Farabollini, 2002); lead to decreased novelty seeking along with increased neophobia (Adriani, Seta, Dessi-Fulgheri, Farabollini & Laviola, 2003); and influence anxiety (Patisaul & Bateman, 2008). In contrast to the abundance of data based on animal models, however, few studies have investigated that childhood behavioral, emotional, and learning development might be altered in human by BPA.

BPA has been repeatedly shown in animals to affect males and females differently (Adriani et al., 2003; Laviola et al., 2005; Xu et al., 2010). On this background, one recent human study examined BPA levels in maternal urine from pregnancy and their association with behavior of their 2-year-old children, and found stronger association with increased externalizing behavior in females than in males (Braun et al., 2009). Such sexually dimorphic results are in accord with the fact that BPA is an estrogen-like chemical with the capacity to bind and act on estrogen receptors. In this study, however, interaction effects between urinary BPA concentration and gender were not significant. This discrepancy is perhaps explained by the possibility that sexually dimorphic behaviors in animals and humans are determined by prenatal rather than pubertal hormones (Auyeung et al., 2009).

As a matter of fact, although the study by Perera et al. (2012) has replicated sexually dimorphic effects of BPA on childhood neurobehavior, it would be worth pointing that the actual finding was inconsistent with the reports by Braun et al. (2009, 2011): among boys, higher prenatal BPA exposure was associated with more behavioral and emotional problems, whereas among girls, higher prenatal BPA exposure was associated with less problems, which is in contrast to the findings by Braun and colleagues showing adverse effects of BPA predominantly in girls (Braun et al., 2009, 2011; Perera et al., 2012). In addition, one recent study using maternal urine samples from pregnancy failed to find a substantial interaction between sex and BPA or phthalate exposures on the children's social behavior (Miodovnik et al., 2011). In terms of postnatal BPA exposure, both the studies by Braun et al. (2009, 2011) and Perera et al. (2012) have found no significant effect modification by child gender.

On the other hand, as interaction terms can be correlated with the original variables, variance inflation might occur and therefore p-values bigger than 0.05 can signify important interactions. Hence, we performed our analyses separately for male and female children, and found that estimated results were not considerably different between both sexes. However, when a quadratic term for urinary BPA level was included in the regression model, the results seemed to be more significant in males than in females (Table S5).

As shown in the quadratic regression results, possible nonlinear patterns were suggested in the association between urinary levels of BPA and mea-

Table 4 Distribution of the CBCL and LDES scores by quartiles of urinary bisphenol A concentration

	Quartile			
N = 1,008	1st	2nd	3rd	4th
CBCL: *M* (*SD*)				
Social withdrawal	54.58 (10.48)	55.26 (10.11)	54.14 (9.20)	55.28 (10.23)
Somatic complaints	52.28 (4.37)	52.75 (4.76)	52.56 (4.51)	52.42 (4.65)
Anxiety/depression	51.58 (3.75)	51.85 (4.74)	52.06 (4.57)	52.47 (5.28)
Social problems	51.65 (3.92)	51.72 (4.57)	52.27 (5.23)	52.89 (5.92)
Thought problems	51.58 (4.88)	51.65 (4.77)	51.34 (3.64)	52.00 (4.38)
Attention problems	51.45 (3.43)	51.71 (4.04)	51.88 (3.94)	52.30 (4.90)
Delinquent behavior	51.01 (2.62)	51.82 (4.98)	52.08 (4.56)	51.37 (3.70)
Aggressive behavior	51.13 (2.87)	51.57 (4.54)	51.90 (4.18)	51.62 (3.88)
Internalizing problems	51.78 (4.00)	51.97 (4.67)	51.94 (4.22)	52.35 (5.08)
Externalizing problems	51.09 (2.72)	51.56 (4.72)	51.94 (4.25)	51.53 (3.76)
Total problems	51.19 (3.08)	51.41 (4.36)	51.74 (3.90)	52.00 (4.62)
LDES: *M* (*SD*)				
Listening	11.57 (2.18)	11.46 (2.25)	11.05 (2.50)	11.12 (2.53)
Thinking	11.50 (1.72)	11.37 (2.00)	11.20 (2.05)	11.15 (2.02)
Speaking	11.62 (2.05)	11.46 (2.23)	11.33 (2.14)	11.37 (2.28)
Reading	11.28 (1.96)	11.15 (2.29)	10.97 (2.21)	10.77 (2.51)
Writing	11.30 (2.10)	11.28 (2.16)	10.97 (2.13)	11.02 (2.27)
Spelling	10.94 (2.30)	10.59 (2.58)	10.57 (2.41)	10.66 (2.64)
Calculations	11.82 (1.56)	11.62 (1.83)	11.73 (1.69)	11.34 (2.15)
Learning quotient	107.84 (9.22)	107.05 (10.20)	106.13 (9.98)	105.88 (11.32)

CBCL, child behavior checklist; LDES, learning disability evaluation scale; SD, standard deviation.

sures of behavioral and learning problems in children, and similar patterns have also been reported from animal studies (Xu et al., 2010) and for outcomes other than neurobehavior (Gualtieri, Iwachow, Venara, Rey & Schteingart, 2011; Jenkins, Wang, Eltoum, Desmond & Lamartiniere, 2011); a nonmonotonic dose–response relationship was proposed for estrogen-like endocrine disruptors (Salonia et al., 2012; Welshons et al., 2003), which complicates our understanding of the biological effects of this chemical. Further work is warranted to acknowledge these nonlinear association patterns.

It would be worthwhile to briefly discuss the distribution of urinary BPA concentrations. The median urinary BPA level in our sample was 1.28 μg/g Cr after Cr-standardization, and the nonstandardized value was 1.23 μg/l, which were lower than the levels from the 2005–2006 NHANES data for 6- to 11-year olds (2.7 ng/ml) or 12- to 19-year olds (2.4 ng/ml), and the levels from the German Environmental Survey on Children (GerES) for 9- to 11-year olds (2.13 μg/l) (Becker et al., 2009; Lakind & Naiman, 2011). The levels were also lower than those observed in recent studies with similar age groups (Teitelbaum et al., 2008; Wolff et al., 2010). Possible reasons for this lower BPA concentration may be different degrees of industrialization or consumption and lifestyle patterns, most likely diet, between Korea and Western countries. Although data are lacking, a study on daily dietary intake of canned food items has shown that estimated human exposure level to BPA was substantially low in Korea (Lim, Kwack, Kim, Kim & Lee, 2009). In addition, urinary BPA concentration may be influenced by the time of day when the sample was collected, with relatively lower values from morning samples (Mahalingaiah et al., 2008). In this study, urine was collected with consistent timing between 9:00 and 11:00 a.m. at school. Moreover, relatively lower LOD (0.15 μg/l) in the current study could have contributed toward lowering the median value (e.g., LOD = 0.4 ng/ml in the 2005–2006 NHANES data; 0.34 ng/ml in Teitelbaum et al.) (Lakind & Naiman, 2011; Teitelbaum et al., 2008). On the other hand, the problem of concentrations below the LOD was negligible in this study, as we were able to measure BPA concentration in every urine sample, and the maximum BPA level was within the range of previous reports (Becker et al., 2009; Braun et al., 2011).

One of the major limitations of this study was that our data were obtained with cross-sectional measurements, through an uncontrolled observational methodology. In a similar context, another important limitation of this study is that no data are available on prenatal exposure to BPA. Given the increased susceptibility of the fetal nervous system during gestation, prenatal BPA exposure is possibly more critical, and recent studies measuring BPA levels both from the mothers during pregnancy and later from the children within their first 5 years of life have indicated that prenatal rather than postnatal BPA exposure was the dominant predictor of neurobehavioral outcomes (Braun et al., 2011; Perera et al., 2012). Accordingly, obtaining repeated BPA measurements throughout different periods of life would have enabled us to identify unique windows of vulnerability to BPA exposure. As a matter of fact, considering the short biological half-life of BPA and

temporal variability of urinary BPA concentration, use of a single urinary BPA measurement that only modestly, at best, reflects prior BPA exposures is in itself an important limitation of this study (Braun et al., 2011, 2012; Mahalingaiah et al., 2008; Teitelbaum et al., 2008). However, some have also supported the use of this biomarker in epidemiologic studies of exposure–health outcome relationships, especially when the study population is large (Teitelbaum et al., 2008; Ye et al., 2011). As the school-age childhood was not sufficiently examined for its potential vulnerability to BPA exposure, we investigated a large community sample of children, and in line with the discussion by Perera et al. (2012), we expected that any noise inherent in a single BPA measurement would bias the findings toward the null (Perera et al., 2012). Finally, although we have controlled for quite a few covariates, potential confounders that need to be further taken into account in future studies include diet, as the major route of BPA exposure is dietary.

In summary, our findings suggest possible adverse impacts of BPA on childhood behavioral and learning development. However, mechanisms underlying the alleged association between BPA and neurobehavior in human still remain to be established. Now, considering the nearly ubiquitous presence of BPA in our environment and also in our body (Becker et al., 2009; Lakind & Naiman, 2011), additional longitudinal studies are pressing.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1 Demographic characteristics of the subjects (detailed)

Table S2 Adjusted Associations between Urinary bisphenol A concentration and the scores from the CBCL and LDES (with weighting adjustment)

Table S3 Adjusted Associations between urinary bisphenol A concentration and the scores from the CBCL and LDES (in male and female children)

Table S4 Quadratic associations between urinary bisphenol A concentration and the scores from the CBCL and LDES (with weighting adjustment)

Table S5 Quadratic associations between urinary bisphenol A concentration and the scores from the CBCL and LDES (in male and female children)

Table S6 Adjusted associations between urinary bisphenol A concentration and the scores from the CBCL and LDES (controlling for different potential confounders)

Table S7 Quadratic associations between urinary bisphenol A concentration and the scores from the CBCL and LDES (controlling for different potential confounders)

Figure S1 Mean CBCL and LDES scores by quartiles of urinary bisphenol A concentration

Acknowledgements

SBH, JWK, and SCC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. No potential conflict of interest relevant to this article was reported. This study was supported by a grant (091-081-059) from the Korean Ministry of Environment (Eco-Technopia 21 Project). The funder had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Correspondence

Soo-Churl Cho, Division of Child and Adolescent Psychiatry, Department of Psychiatry, Seoul National University College of Medicine, 101 Daehak-No, Chongno-Gu, Seoul, Korea; Email: soochurl@snu.ac.kr

Key points

- Bisphenol A has been repeatedly shown in animals to affect multiple features of neurobehavior, but few studies have investigated environmentally relevant, low-dose exposure to BPA in relation to human neurobehavior.
- Urinary BPA concentration might be associated with multiple features of childhood neurobehavior, possibly contributing to maladaptive behavior and problematic learning in school-age children.
- A nonmonotonic dose–response relationship was suggested between BPA exposure and childhood neurobehavior, which warrants further work for our understanding of the biological effects of this chemical.
- Considering the nearly ubiquitous presence of BPA in our environment and also in our body, continuing controversies over the safety of BPA should be properly addressed with further studies.

References

Achenbach, T.M. (1991). *Manual for the Child Behavior Checklist/4–18 and 1991 Profile*. Burlington, VT: University of Vermont, Department of Psychiatry.

Adriani, W., Seta, D.D., Dessi-Fulgheri, F., Farabollini, F., & Laviola, G. (2003). Altered profiles of spontaneous novelty seeking, impulsive behavior, and response to D-amphetamine in rats perinatally exposed to bisphenol A. *Environmental Health Perspectives*, *111*, 395–401.

Auyeung, B., Baron-Cohen, S., Ashwin, E., Knickmeyer, R., Taylor, K., Hackett, G., & Hines, M. (2009). Fetal testosterone

predicts sexually differentiated childhood behavior in girls and in boys. *Psychological Science*, *20*, 144–148.

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., & Pirkle, J.L. (2005). Urinary creatinine concentrations in the U.S. population: Implications for urinary biologic monitoring measurements. *Environmental Health Perspectives*, *113*, 192–200.

Becker, K., Goen, T., Seiwert, M., Conrad, A., Pick-Fuss, H., Muller, J., … & Kolossa-Gehring, M. (2009). GerES IV: Phthalate metabolites and bisphenol A in urine of German children. *International Journal of Hygiene and Environmental Health*, *212*, 685–692.

Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Yolton, K., Ye, X., Dietrich, K.N., & Lanphear, B.P. (2011). Impact of early-life bisphenol A exposure on behavior and executive function in children. *Pediatrics*, *128*, 873–882.

Braun, J.M., Smith, K.W., Williams, P.L., Calafat, A.M., Berry, K., Ehrlich, S., & Hauser, R. (2012). Variability of urinary phthalate metabolite and bisphenol A concentrations before and during pregnancy. *Environmental Health Perspectives*, *120*, 739–745.

Braun, J.M., Yolton, K., Dietrich, K.N., Hornung, R., Ye, X., Calafat, A.M., & Lanphear, B.P. (2009). Prenatal bisphenol A exposure and early childhood behavior. *Environmental Health Perspectives*, *117*, 1945–1952.

Calafat, A.M., Ye, X., Wong, L.Y., Reidy, J.A., & Needham, L.L. (2008). Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. *Environmental Health Perspectives*, *116*, 39–44.

Cho, S.C., Kim, B.N., Hong, Y.C., Shin, M.S., Yoo, H.J., Kim, J.W., … & Kim, H.W. (2010). Effect of environmental exposure to lead and tobacco smoke on inattentive and hyperactive symptoms and neurocognitive performance in children. *Journal of Child Psychology and Psychiatry*, *51*, 1050–1057.

Dessi-Fulgheri, F., Porrini, S., & Farabollini, F. (2002). Effects of perinatal exposure to bisphenol A on play behavior of female and male juvenile rats. *Environmental Health Perspectives*, *110* (Suppl. 3), 403–407.

Fujimoto, T., Kubo, K., & Aou, S. (2006). Prenatal exposure to bisphenol A impairs sexual differentiation of exploratory behavior and increases depression-like behavior in rats. *Brain Research*, *1068*, 49–55.

Gualtieri, A.F., Iwachow, M.A., Venara, M., Rey, R.A., & Schteingart, H.F. (2011). Bisphenol A effect on glutathione synthesis and recycling in testicular Sertoli cells. *Journal of Endocrinological Investigation*, *34*, e102–e109.

Ishido, M., Masuo, Y., Kunimoto, M., Oka, S., & Morita, M. (2004). Bisphenol A causes hyperactivity in the rat concomitantly with impairment of tyrosine hydroxylase immunoreactivity. *Journal of Neuroscience Research*, *76*, 423–433.

Jenkins, S., Wang, J., Eltoum, I., Desmond, R., & Lamartiniere, C.A. (2011). Chronic oral exposure to bisphenol A results in a nonmonotonic dose response in mammary carcinogenesis and metastasis in MMTV-erbB2 mice. *Environmental Health Perspectives*, *119*, 1604–1609.

Kaufman, A.S. (1976). A four test short form of the WISC-R. *Comtemporary Educational Psychology*, *1*, 180–196.

Kawai, K., Nozaki, T., Nishikata, H., Aou, S., Takii, M., & Kubo, C. (2003). Aggressive behavior and serum testosterone concentration during the maturation process of male mice: The effects of fetal exposure to bisphenol A. *Environmental Health Perspectives*, *111*, 175–178.

Kessler, R.C., Berglund, P., Chiu, W.T., Demler, O., Heeringa, S., Hiripi, E., … & Zheng, H. (2004). The US National Comorbidity Survey Replication (NCS-R): Design and field procedures. *Int J Methods Psychiatr Res*, *13*, 69–92.

Kim, B.N., Cho, S.C., Kim, Y., Shin, M.S., Yoo, H.J., Kim, J.W., … & Hong, Y.C. (2009). Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. *Biological Psychiatry*, *66*, 958–963.

Kim, M.K., & Kim, Z.S. (1986). A study on the abbreviated form of the K-WISC. *The Seoul Journal of Psychiatry*, *11*, 194–201.

Kim, Y., Kim, B.N., Hong, Y.C., Shin, M.S., Yoo, H.J., Kim, J.W., … & Cho, S.C. (2009). Co-exposure to environmental lead and manganese affects the intelligence of school-aged children. *Neurotoxicology*, *30*, 564–571.

Lakind, J.S., & Naiman, D.Q. (2011). Daily intake of bisphenol A and potential sources of exposure: 2005–2006 National Health and Nutrition Examination Survey. *Journal of Exposure Science & Environmental Epidemiology*, *21*, 272–279.

Laviola, G., Gioiosa, L., Adriani, W., & Palanza, P. (2005). D-amphetamine-related reinforcing effects are reduced in mice exposed prenatally to estrogenic endocrine disruptors. *Brain Research Bulletin*, *65*, 235–240.

Leranth, C., Szigeti-Buck, K., Maclusky, N.J., & Hajszan, T. (2008). Bisphenol A prevents the synaptogenic response to testosterone in the brain of adult male rats. *Endocrinology*, *149*, 988–994.

Lim, D.S., Kwack, S.J., Kim, K.B., Kim, H.S., & Lee, B.M. (2009). Risk assessment of bisphenol A migrated from canned foods in Korea. *Journal of Toxicology and Environmental Health. Part A*, *72*, 1327–1335.

Mahalingaiah, S., Meeker, J.D., Pearson, K.R., Calafat, A.M., Ye, X., Petrozza, J., & Hauser, R. (2008). Temporal variability and predictors of urinary bisphenol A concentrations in men and women. *Environmental Health Perspectives*, *116*, 173–178.

Matsumoto, A., Kunugita, N., Kitagawa, K., Isse, T., Oyama, T., Foureman, G.L., … & Kawamoto, T. (2003). Bisphenol A levels in human urine. *Environmental Health Perspectives*, *111*, 101–104.

McCarney, S.B. (1996). *The Learning Disability Evaluation Scale-renormed*. Columbia, MO: Hawthorne Educational Services.

Miodovnik, A., Engel, S.M., Zhu, C., Ye, X., Soorya, L.V., Silva, M.J., … & Wolff, M.S. (2011). Endocrine disruptors and childhood social impairment. *Neurotoxicology*, *32*, 261–267.

Negishi, T., Kawasaki, K., Suzaki, S., Maeda, H., Ishii, Y., Kyuwa, S., … & Yoshikawa, Y. (2004). Behavioral alterations in response to fear-provoking stimuli and tranylcypromine induced by perinatal exposure to bisphenol A and nonylphenol in male rats. *Environmental Health Perspectives*, *112*, 1159–1164.

Oh, K.J., & Lee, H.R. (1990). *Development of Korean version of child behavior checklist (K-CBCL)*. Seoul: Korean Research Foundation Report.

Palanza, P., Gioiosa, L., vom Saal, F.S., & Parmigiani, S. (2008). Effects of developmental exposure to bisphenol A on brain and behavior in mice. *Environmental Research*, *108*, 150–157.

Panzica, G.C., Viglietti-Panzica, C., Mura, E., Quinn, M.J., Jr, Lavoie, E., Palanza, P., & Ottinger, M.A. (2007). Effects of xenoestrogens on the differentiation of behaviorally-relevant neural circuits. *Frontiers in Neuroendocrinology*, *28*, 179–200.

Park, K.S., Yoon, J.Y., Park, H.J., Park, H.J., & Kwon, K.U. (1996). *Development of KEDI-WISC, individual intelligence test for Korean children*. Seoul: Korean Educational Development Institute.

Patisaul, H.B., & Bateman, H.L. (2008). Neonatal exposure to endocrine active compounds or an ERbeta agonist increases adult anxiety and aggression in gonadally intact male rats. *Hormones and Behavior*, *53*, 580–588.

Perera, F., Vishnevetsky, J., Herbstman, J.B., Calafat, A.M., Xiong, W., Rauh, V., & Wang, S. (2012). Prenatal bisphenol A exposure and child behavior in an inner-city cohort. *Environmental Health Perspectives*, *120*, 1190–1194.

Rothman, K.J. (1990). No adjustments are needed for multiple comparisons. *Epidemiology*, *1*, 43–46.

Roy, J.R., Chakraborty, S., & Chakraborty, T.R. (2009). Estrogen-like endocrine disrupting chemicals affecting puberty in humans – A review. *Medical Science Monitor*, *15*, RA137–RA145.

Salonia, A., Abdollah, F., Capitanio, U., Suardi, N., Briganti, A., Gallina, A., … & Montorsi, F. (2012). Serum sex steroids depict a nonlinear u-shaped association with high-risk prostate cancer at radical prostatectomy. *Clinical Cancer Research*, *18*, 3648–3657.

Shin, M.S., Hong, K.E., Kim, Z.S., & Cho, S.C. (1998). A standardization study of the Korean version of Learning Disability Evaluation Scale. *Journal of Korean Neuropsychiatric Association*, *37*, 1233–1245.

Teitelbaum, S.L., Britton, J.A., Calafat, A.M., Ye, X., Silva, M.J., Reidy, J.A., … & Wolff, M.S. (2008). Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens and phenols among minority children in the United States. *Environmental Research*, *106*, 257–269.

Welshons, W.V., Thayer, K.A., Judy, B.M., Taylor, J.A., Curran, E.M., & vom Saal, F.S. (2003). Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. *Environmental Health Perspectives*, *111*, 994–1006.

Wolff, M.S., Teitelbaum, S.L., Pinney, S.M., Windham, G., Liao, L., Biro, F., … & Calafat, A.M. (2010). Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls. *Environmental Health Perspectives*, *118*, 1039–1046.

Xu, X.H., Zhang, J., Wang, Y.M., Ye, Y.P., & Luo, Q.Q. (2010). Perinatal exposure to bisphenol-A impairs learning-memory by concomitant down-regulation of N-methyl-D-aspartate receptors of hippocampus in male offspring mice. *Hormones and Behavior*, *58*, 326–333.

Ye, X., Wong, L.Y., Bishop, A.M., & Calafat, A.M. (2011). Variability of urinary concentrations of bisphenol A in spot samples, first morning voids, and 24-hour collections. *Environmental Health Perspectives*, *119*, 983–988.

Accepted for publication: 13 December 2012
Published online: 28 February 2013