Published in final edited form as:
Environ Res. 2013 October ; 126: 43–50. doi:10.1016/j.envres.2013.06.004.

Prenatal and Early Childhood Bisphenol A Concentrations and Behavior in School-Aged Children

Kim G. Harley[a], **Robert B. Gunier**[a], **Katherine Kogut**[a], **Caroline Johnson**[a], **Asa Bradman**[a], **Antonia M. Calafat**[b], and **Brenda Eskenazi**[a]

[a]Center for Environmental Research and Children's Health (CERCH), School of Public Health, University of California, 1995 University Ave, Suite 265, Berkeley, CA 94704 USA

[b]Division of Laboratory Sciences, National Center for Environmental Health, Centers for, Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333 USA

Abstract

Introduction—Early life exposure to bisphenol A (BPA), an endocrine disrupting chemical used in some food and beverage containers, receipts, and dental sealants, has been associated with anxiety and hyperactivity in animal studies. A few human studies also show prenatal and childhood BPA exposure to be associated with behavior problems in children.

Methods—We measured BPA in urine from mothers during pregnancy and children at 5 years of age (N = 292). Child behavior was assessed by mother and teacher report at age 7 years and direct assessment at age 9 years.

Results—Prenatal urinary BPA concentrations were associated with increased internalizing problems in boys, including anxiety and depression, at age 7. No associations were seen with prenatal BPA concentrations and behaviors in girls. Childhood urinary BPA concentrations were associated with increased externalizing behaviors, including conduct problems, in girls at age 7 and increased internalizing behaviors and inattention and hyperactivity behaviors in boys and girls at age 7.

Conclusions—This study adds to the existing literature showing associations of early life BPA exposure with behavior problems, including anxiety, depression, and hyperactivity in children. Additional information about timing of exposure and sex differences in effect is still needed.

Keywords

Bisphenol A; behavior; ADHD; anxiety; depression; children

Corresponding author: Dr. Kim Harley, Center for Environmental Research and Children's Health (CERCH), School of Public Health, University of California, Berkeley, 1995 University Ave, Suite 265, Berkeley, CA 94704, Tel: +1 510 643-1310, Fax: +1 510 642-9083, kharley@berkeley.edu.

Disclaimer
The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Human Subjects
All activities were approved by the Committee for the Protection of Human Subjects at the University of California Berkeley under human subjects protocol numbers 2010-03-949 and 2010-01-620, and the Centers for Disease Control and Prevention.

1. Introduction

Bisphenol A (BPA) is an endocrine-disrupting compound used in the manufacture of polycarbonate plastics and epoxy resins and as an additive in thermal paper. Humans are exposed to BPA via plastic food and beverage containers, canned food, medical devices, dental sealants, and receipts (Biedermann et al., 2010; Geens et al., 2011). Exposure to BPA is nearly ubiquitous, with 95% of Americans participating in the National Health and Nutrition Examination Survey (NHANES) having detectable levels of BPA in their urine (Calafat et al., 2008).

In animal studies, gestational exposure to BPA has been associated with alterations in brain morphology, function, and behavior (Wolstenholme et al., 2011). In rats and mice, perinatal BPA exposure has been shown to feminize sexually dimorphic regions of the hypothalamus in males (Patisaul et al., 2006; Rubin et al., 2006) and masculinize these regions in females (Patisaul et al., 2007). Studies have also found loss of sex differences in rodent behavior (Cox et al., 2010; Nakagami et al., 2009; Rubin et al., 2006), including rearing, exploration, and mother-infant interactions. Several studies have found gestational BPA exposure in rodents to be associated with increased anxiety (Cox et al., 2010; Patisaul and Bateman, 2008; Ryan and Vandenbergh, 2006; Tian et al., 2010; Xu et al., 2011; Yu et al., 2011) and hyperactivity (Ishido et al., 2004; Ishido et al., 2007; Masuo et al., 2004; Xu et al., 2007), although there is less consistency about whether these effects are present in males, females, or both.

Several human studies have investigated the role of prenatal BPA exposure on behavior in children (Braun et al., 2011; Braun et al., 2009; Miodovnik et al., 2011; Perera et al., 2012; Yolton et al., 2011). In a sociodemographically diverse population, Braun et al found that maternal urinary BPA concentrations during pregnancy were associated with increased behavior problems in girls, but not boys, according to maternal report on the Behavioral Assessment Scale for Children (BASC-2) (Braun et al., 2011; Braun et al., 2009). Specifically, higher prenatal urinary BPA concentrations were associated with more externalizing problem behaviors in girls at age 2 years (Braun et al., 2009) and increased report of hyperactivity, anxiety, and depression behaviors in girls at age 3 (Braun et al., 2011). In contrast, in a low-income African-American population, Perera et al found that maternal urinary BPA concentrations during pregnancy were associated with fewer behavior problems (anxious/depressed, aggressive behavior) in girls but increased aggressive behavior and emotional reactivity in boys between 3 and 5 years of age, according to maternal report on the Child Behavior Check List (CBCL) (Perera et al., 2012). Miodovnik et al found suggestive, but non-significant associations of prenatal BPA concentrations with social responsiveness, or autistic spectrum-type behaviors, in another cohort of predominantly minority women (Miodovnik et al., 2011).

Two of the above-mentioned studies also examined post-natal BPA exposure (Braun et al., 2011; Perera et al., 2012), but found no association of children's urinary BPA concentrations between age 1 and 4 years with later behavior. However, in a randomized trial of dental restorations, children with higher cumulative exposure to BPA, categorized as surface-years of exposure to BPA-containing dental composites between 6 and 10 years of age, reported more anxiety, depression, maladjustment, and emotional symptoms on the self-reported BASC between age 11 and 16 years compared to children randomized to receive amalgam or non-BPA dental restorations (Maserejian et al., 2012). This study found no differences by sex.

The present study examined the association of BPA concentrations in maternal urine during pregnancy and in children's urine at age 5 years with mother- and teacher-reported behavior

problems at age 7 and interviewer-administered tests of attention and hyperactivity at age 9. Based on previous animal and human literature, behaviors of particular interest were anxiety, depression, aggression, and hyperactivity.

2. Materials and Methods

2.1 Study Population

Data were collected from mothers and children participating in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal birth cohort study examining the role of environmental exposures on the health of pregnant women and their children. In 1999–2000, we enrolled 601 pregnant women living in the Salinas Valley, an agricultural region of California. Eligible women were less than 20 weeks gestation, were at least 18 years of age, qualified for low-income health insurance (MediCal), spoke English or Spanish, and were receiving prenatal care at one of 6 participating clinics serving the region's low-income, farmworker population. A total of 527 women were followed through the birth of a singleton, live born infant, and behavioral data at ages 7 and 9 years are available for 349 and 309 of these children, respectively. We excluded 3 children diagnosed with developmental disabilities (Down syndrome, autism, hydrocephaly), 1 deaf child, and 53 children missing BPA measures (7 were missing prenatal and 46 were missing early childhood urinary BPA concentrations). The final sample was 292 children with both prenatal and childhood BPA concentrations and behavior data at 7 and/or 9 years of age. All study activities were approved by the Committees for the Protection of Human Subjects at U.C. Berkeley and the Centers for Disease Control and Prevention (CDC).

2.2 Urinary BPA Concentrations

Spot urine samples were collected in 1999–2000 from mothers at two time points during pregnancy (mean ± sd: 13.6 ± 4.8 and 26.4 ± 2.5 weeks gestation) and from children at 5 years of age (mean ± sd: 5.0 ± 0.2 years). Urine samples were collected in polypropylene urine cups, aliquotted into glass vials, and frozen at −80°C. Samples were shipped to the CDC for analysis.

Total urinary BPA concentration (conjugated plus unconjugated) was measured using online solid phase extraction coupled to high performance liquid chromatography-isotope dilution tandem mass spectrometry (Ye et al., 2005). The limit of detection (LOD) was 0.4 μg/L. Concentrations below the LOD for which a signal was detected were reported as measured. Concentrations below the LOD with no signal detected were randomly imputed based on a log-normal probability distribution using maximum likelihood estimation (Lubin et al., 2004). Each batch of study samples also included analytical standards, reagent blanks, and matrix-based quality control (QC) materials at two concentrations (~10 μg/L and ~2.5 μg/L). The method accuracy, expressed as a spiked recovery percentage, ranged from 98 to 113% at four different spiking levels (Ye et al., 2005). The method precision, determined from the coefficients of variation of repeated measurements of the QC materials was below 10%.

Specific gravity was measured with a refractometer (National Instrument Company Inc., Baltimore, MD) for the maternal urine samples, but was unavailable for the children's samples. Thus, maternal concentrations were normalized for urinary dilution using urine specific gravity (Mahalingaiah et al., 2008) and child BPA concentrations were normalized by dividing by urinary creatinine concentration.

For the prenatal samples, the two urinary measures were available for 221 women and were averaged to better approximate exposure over the course of pregnancy. In the 71 women for whom only one BPA measurement was available, the single measurement was used. For children, the single measure of urinary BPA concentration at 5 years of age was used.

2.3 Childhood behavior

Children's behavior was assessed by maternal and teacher report at age 7 and by direct assessment at age 9.

At 7 years of age, the Behavior Assessment System for Children 2 (BASC-2) (Reynolds and Kamphaus, 2004) and the Conners' ADHD/DSM-IV Scales (CADS) (Conners, 2001) were interviewer-administered to the mother (due to low literacy rates) and self-administered by the child's teacher. Both instruments have been validated in English and Spanish. The BASC-2 Parent Rating Scale asks how often the child exhibits certain behaviors in the home setting (160 questions) while the Teacher Rating Scale asks about similar behaviors at school (139 questions). Frequencies were summed into raw scores and compared to national norms to generate agestandardized T-scores for several clinical scales, with higher values indicating more frequent problem behaviors. Scales of interest from the BASC-2 were anxiety, depression, and somatization (which can be combined into the internalizing problems composite scale); aggression, conduct problems, and hyperactivity (combined into the externalizing problems composite scale); and attention problems. The CADS Parent and Teacher Forms assess attention and hyperactivity using 26 questions that correspond to the DSM-IV criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). Answers were summed into raw scores and compared to national norms to generate T-scores standardized for age and sex for three DSM-IV-oriented scales (inattention, hyperactivity, and ADHD DSM-IV scales).

At 9 years of age, we also assessed ADHD directly using the Connors' Continuous Performance Test (CPT), a computerized test that assesses reaction time, accuracy, and impulse control by having the child press the space bar as quickly as possible when any letter except the letter × appears on the screen (Conners and Staff, 2001). This program yields age- and sexstandardized T-scores for errors of commission (i.e. failure to withhold the response for an X, suggesting lack of response inhibition), errors of omission (i.e. failure to respond to other letters, suggesting inattention), reaction time, reaction time variability, and response bias (β, a measure of response style with high scores indicating a more cautious style).

2.4 Covariates

Information about possible confounders was gathered through structured maternal interviews conducted in English or Spanish by trained interviewers. During pregnancy, we gathered information about maternal age, race/ethnicity, education level, marital status, country of birth, years of residence in the United States and health behaviors, including smoking during pregnancy. Maternal interviews when the children were 7 years old assessed factors that might impact child behavior or mothers' perception of child behavior, including number of siblings in the home, family income, maternal depression, and the level of stimulation in the home environment. Family income was compared to the federal poverty threshold for families of the same size to generate a variable for ≤ poverty vs. > poverty. Maternal depression was assessed using the Center for Epidemiologic Studies - Depression (CES-D) scale (Radloff, 1977) and analyzed as depressed vs. not depressed (≥16 vs. <16). The caregiving environment and level of stimulation was assessed using the Home Observation for Measurement of the Environment (HOME) Inventory (Caldwell and Bradley, 1984). HOME score, age and parity were included in multivariable models as continuous variables. All other covariates were categorized as shown in Table 1.

Because the study participants are from an agricultural region and because we have previously found prenatal exposure to organophosphate pesticides to be associated with attention problems in this cohort (Marks et al., 2010), we also controlled for maternal

urinary concentrations of dialkyl phosphate (DAP) metabolites of organophosphate pesticides. DAP metabolites were measured in the same maternal urine samples as BPA using isotope dilutions gas chromatography-tandem mass spectrometry (Bradman et al., 2005) and were averaged to approximate exposure throughout pregnancy. Polybrominated diphenyl ether (PBDE) flame retardants are also an important exposure in this population that has been associated with neurobehavior (Eskenazi et al. 2012). However, because PBDEs were not associated with BPA concentrations and controlling for PBDEs did not change the association of BPA and behavior, PBDE concentrations were not included in the final models.

2.5 Statistical Analysis

T-scores for all behavioral outcomes were examined as continuous variables. We first generated descriptive statistics for all of the outcome measures separately by sex and examined the distributions of these variables. T-scores for the BASC-2 and CADS are standardized to a mean=50 and SD=10 and descriptive analyses of the behavioral outcomes showed similar distributions in this population.

We examined the functional form of the relationships of BPA concentrations with each outcome variable using lowess plots. We used generalized additive models (GAM) with a 3-degrees-of-freedom cubic spline to evaluate the linearity of exposure-response curves and found that most relationships did not depart from linearity. Thus, BPA concentration was analyzed as a continuous variable in the main analyses, although we also re-ran our models results examining BPA concentration quartiles. Continuous urinary BPA concentrations were log-transformed to reduce the influence of outliers and to better improve the functional form of the association. Because of the relatively small range of prenatal urinary BPA concentrations (<LOD to 33) we log-transformed to the base 2. Thus, associations are for the change in outcome for each twofold increase in urinary BPA concentration.

Multivariable linear regression was used to examine the association of maternal and child BPA concentrations with continuous behavioral outcomes. Because animal and epidemiologic studies suggest that the effects of BPA exposure on behavior differ for males and females, we included interaction terms for sex in all models of the total population, and then conducted analyses stratified by boys and girls. Both maternal and child BPA concentrations were included in all models.

We conducted several sensitivity analyses to ensure that the findings were robust. First, we examined maternal and child BPA concentrations in separate models rather than together in the same model. Second, we examined issues of urinary dilution by excluding samples with creatinine concentrations <20 mg/dL (N=17) and including BPA concentrations unadjusted for urinary dilution in the models. Third, we examined raw CADS and CPT scores using negative binomial regression (for count data) rather than T-scores. Fourth, we excluded outliers identified by the extreme studentized deviate many-outlier procedure (Rosner, 1983). Finally, we examined for bias due to loss to follow-up using inverse probability weighting. All analyses were conducted in Stata 11.

3. Results

Demographic characteristics of the study population are shown in Table 1. Mothers tended to be young (75% were less than 30), married (83%), Latina (99%) and born in Mexico (86%). Only 22% of mothers had graduated from high school and most families (70%) were living below the federal poverty threshold. Many women (28%) reported sufficient symptoms at the 7-year follow-up visit to qualify as depressed on the CES-D scale. Few factors were associated with urinary BPA concentrations, although mothers who were born

in the United States, who had lived longer in the United States, or who had more children had higher BPA concentrations than other mothers (Quiros-Alcala, submitted).

Mean BPA concentrations in the children at age 5 years were approximately twice as high as in their mothers during pregnancy (Table 2). However, BPA concentrations in this population were considerably lower than in the general U.S. population. The geometric mean BPA concentration was 1.1 μg/L in pregnant mothers (compared to 2.4 μg/L for all women in NHANES 2003–2004) and 2.5 μg/L for 5-year old children (compared to 3.6 μg/L for children aged 6–11 in NHANES)(Calafat et al., 2008). The two prenatal BPA concentrations were weakly correlated (r=0.25, p-value=0.001), unstandardized prenatal and child BPA concentrations were not (r=0.02, p-value=0.79).

3.1 Prenatal BPA exposure

The association of prenatal BPA concentrations with child behavior as assessed by the BASC-2 and CADS is shown in Table 3. We observed significant interaction by sex for the association of prenatal BPA concentrations with many of the subscales; thus, results from sexstratified models are shown.

In boys, higher maternal urinary BPA concentrations during pregnancy were associated with increased internalizing problems at age 7 years according to both mother and teacher report. Each doubling of prenatal BPA concentrations was associated with an increase in internalizing scores of 1.8 points (95% CI: 0.3, 3.3) by mothers' report and 2.5 points (95% CI: 0.7, 4.4) by teachers' report. Both mothers and teachers reported increased symptoms of depression and anxiety in boys with higher prenatal BPA concentrations. The findings were also suggestive of increased somatization in boys by mothers' report but these findings were not statistically significant. Increasing prenatal BPA concentrations were also associated with increased aggressive behavior in boys according to teacher report (Table 3).

Prenatal BPA concentrations were not associated with inattention or hyperactivity in boys or girls on the CADS at age 7. Similarly, prenatal BPA concentrations were not associated with errors of omission, errors of commission, reaction time variability or ADHD confidence index on the CPT at 9 years of age (supplemental Table 1).

No associations were seen with prenatal BPA concentrations and any behaviors in girls, although for almost all scales, the point estimates trended towards increased behavior problems in boys and decreased in girls.

3.2 Childhood BPA exposure

Associations of childhood urinary BPA concentrations at age 5 with behavior at age 7 are shown in Table 4. Teachers' report showed similar findings to prenatal exposure in boys, with childhood BPA concentrations associated with increased internalizing scores and increased anxiety on the BASC-2. Childhood BPA concentrations were also associated with attention problems in boys by teacher report on both the BASC-2 and the CADS. However, no associations between childhood BPA concentrations and any behaviors in boys were seen according to maternal report.

In girls, childhood urinary BPA concentrations were associated with internalizing problems (by teacher report) and externalizing problems (by mother and teacher report). Each doubling of BPA concentration at age 5 was associated with an increase in externalizing score of 1.2 (95% CI: 0.3, 2.1) by maternal report and 1.0 (95% CI: −0.1, 2.0) by teacher report, with teachers additionally reporting associations with hyperactivity and mothers reporting associations with conduct problems. Each doubling of urinary BPA concentrations at age 5 in girls was associated with an increase in ADHD score of 1.3 (95% CI: 0.4, 2.2) by

maternal report and 1.7 (0.3, 3.1) by teacher report on the CADS, with associations also seen for both inattention and hyperactivity behaviors. However, no associations were seen with 5 year BPA concentrations and any ADHD parameters measured in the CPT (Table S2).

Because the interaction terms for sex were not statistically significant for childhood BPA concentrations and teacher-reported behavior (Table 4), we analyzed boys and girls together to increase the sample size (Table S3). All associations persisted and became more statistically significant: childhood urinary BPA concentrations were associated with increased scores for internalizing problems (β = 1.6; 95% CI: 0.5, 2.8), anxiety (β = 1.4; 95% CI: 0.3, 2.5), depression (β = 1.2; 95% CI: 0.3, 2.2), hyperactivity (β = 1.1; 95% CI: 0.0, 2.1), and inattention (β = 0.9; 95% CI: 0.3, 1.5) on the BASC-2, as well as inattention (β = 1.4; 95% CI: 0.5, 2.2)and ADHD (β = 1.3; 95% CI: 0.3, 2.2) on the CADS.

3.3 Sensitivity Analyses

In general, the findings were robust in sensitivity analyses. When we examined prenatal and childhood BPA concentrations in separate models, the findings were largely unchanged, suggesting that effects of prenatal and postnatal BPA exposure are independent of each other. Findings also changed little when we accounted for urinary dilution either by dropping individuals with dilute urine or examining BPA concentrations unadjusted for creatinine or specific gravity. The associations of prenatal and, particularly, childhood BPA concentrations also persisted regardless of whether sex-standardized T-scores or raw scores were used. Findings also changed little when outliers and influential points were removed. Finally, using inverse probability weighting to account for potential bias due to loss to follow-up did not meaningfully change the results.

4. Discussion

We found that higher urinary BPA concentrations in mothers during pregnancy were associated with increased internalizing problem behaviors, including anxiety and depression, in their sons at 7 years of age. Higher urinary BPA concentrations in the children at age 5 were associated with increased internalizing problems and increased ADHD behaviors in both boys and girls and increased externalizing behaviors, including conduct problems, in girls at age 7. Findings of associations with prenatal BPA concentrations and behavior problems in boys were consistent using both mothers' and teachers' report, but many associations with childhood BPA concentrations were only seen with teacher report. The different results observed for mother and teacher report of internalizing problems with childhood BPA levels may be due to differences between home and school setting (Achenbach et al. 1987), and suggest that some behavior problems may need to be considered as informant-specific phenomena (Offord et al. 1996). Although associations were seen with both mother and teacher reports of attention and hyperactivity, no associations were seen with direct assessment of ADHD behaviors using the CPT.

This study adds to the limited and somewhat conflicting data on the effects of prenatal and postnatal BPA exposure on children's neurobehavioral development. Including the present study, five epidemiologic papers from four different studies have examined internalizing, externalizing, and attention outcomes in children, three relying on urinary biomonitoring measures (Braun et al., 2011; Braun et al., 2009; Perera et al., 2012) and one on indirect measures of exposure (Maserejian et al., 2012) (see Table 5). All four studies have found associations of BPA exposure and behavior problems in children, with three studies specifically seeing increased anxiety and depression. However, there is little consistency about whether these effects are in boys or girls and a lack of agreement about the relevant timing of exposure. While Braun et al reported that *prenatal* urinary BPA concentrations were associated with behavior problems in girls only, our study and Perera et al found

associations with behavior problems in boys. Braun et al and Perera et al found no associations of *childhood* urinary BPA concentrations with later behavior. However, using different study designs and exposure and outcome measures, our study and Maserejian et al both found BPA exposure in childhood to be associated with anxiety and depression in boys and girls. Maserejian et al found additional associations with personal/clinical maladjustment and emotional problems while we found associations with externalizing/conduct problems, inattention, and hyperactivity.

The animal studies have focused on perinatal BPA exposure, shedding little light on the effects of exposure later in development. Even so, some discrepancies with regard to sex are seen. Namely, two studies found increased anxiety in females and decreased anxiety in male rodents (Farabollini et al., 1999; Yu et al., 2011), while another found the opposite (decreased anxiety in females and increased anxiety in males)(Xu et al., 2011). Difference in findings may be a result of different doses, timing, species, and strains. However, one consistency is that in each of these cases the authors report a loss of sexually-dimorphic differences in BPA exposed animals; that is, sex differences in anxiety-like behaviors in controls were eliminated in the BPA exposed group. Thus, one possible explanation for the different findings observed for prenatal BPA exposure in humans is that sex differences are reduced. For example, Braun et al found that prenatal BPA concentrations were associated with increased externalizing behaviors (typically more common in boys) among girls while we report increased internalizing behaviors (more common in girls) among boys, suggesting boys' and girls' behavior might be becoming more similar with higher prenatal BPA concentrations. However, this does not explain our finding and that of Perera et al of increased aggression in boys, or Braun et al's additional finding of increased internalizing behaviors in girls.

Development of sex-specific behavior is mediated largely by sex hormones in the fetal brain (Patisaul and Polston, 2008) and exposure to endocrine-disrupting compounds during earliest development can impact behavior, including aggression and anxiety, in both males and females (Patisaul and Bateman, 2008). In female mice, perinatal exposure to ethinyl estradiol at 5 μg/kg/day and BPA at 200 μg/kg/day were both associated with increased anxiety on the elevated plus maze and light/dark chamber, suggesting an estrogenic mechanism of anxiety (Ryan and Vandenbergh, 2006). However neonatal exposure to BPA at 50 μg/kg/day (but not the same dose of estradiol) also increased anxiety-like behaviors in male rats (Patisaul and Bateman, 2008). Among Wistar rats prenatally dosed with 40 μg/kg/day of BPA, both males and females had elevated corticosterone levels compared to controls after a mildly stressful maze test, with BPA-exposed females also exhibiting elevated basal corticosterone levels and more anxiety on the Y maze (Poimenova et al., 2010).

BPA may also impact anxiety, hyperactivity, and attention through dopaminergic pathways. Perinatal exposure to low doses (250 ng/kg/day) of BPA increased anxiety-like behavior and increased dopamine levels in male but not female mice in one study (Matsuda et al., 2012). In another study, BPA exposure to male rats during lactation was associated with hyperactivity, as measured by increased spontaneous motor activity, accompanied by reductions in tyrosine hydroxylase immunoreactivity in the substantia nigra, suggesting degeneration of dopaminergic neurons (Ishido et al., 2007). A third study found that rats dosed perinatally with 2 μg/kg/day of BPA exhibited increased hyperactivity (indicated by greater moved distance) and decreased attention (indicated by higher rearing frequency), possibly caused by GABAergic disinhibition and dopaminergic enhancement (Zhou et al., 2011). Thus, biological mechanisms exist to support the findings observed in this study.

The present study has some limitations. BPA was measured in two urine samples collected during pregnancy in 1999–2000 and one urine sample collected at age 5 in 2005–2006.

Studies indicate considerable intra- and inter-day variability (Ye et al., 2011), suggesting that the urinary BPA concentrations used in this study may not represent on-going BPA exposure. This may be a bigger issue in the measure of childhood BPA exposure than prenatal exposure, since childhood exposure is represented by just one spot urine sample and reflects a longer time span. In our data, the two prenatal BPA measurements were only weakly correlated. The median and range of BPA concentrations in this study were relatively low compared to the general U.S. population, potentially limiting our ability to detect associations, and possibly explaining the differences in findings among studies. We conducted multiple comparisons and cannot rule out the possibility that some associations were due to chance. However, strengths of this study include the use of biomarkers to assess early life BPA exposure, behavior assessed by multiple observers at school age, and information on a wide variety of potential confounders.

Overall, this study supports findings in the animal and human literature linking prenatal and childhood BPA exposure to behavior problems, including anxiety, depression, and hyperactivity. However, there are considerable inconsistencies in the literature with regard to the timing of the critical period of exposure and whether one sex is more vulnerable to the effects of BPA. . Other measures to accurately characterize on-going BPA exposure over pregnancy and early childhood are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Xiaoyun Ye, Xiaoliu Zhou, Tao Jia, and Ryan Hennings for measuring the urinary BPA concentrations and Subha Venkat and Karen Huen for their help with the biological samples.

Funding Sources

This work was supported by grants 1RC2 ES018792 and PO1 ES009605 from the National Institute of Environmental Health Sciences and grants R82670901, RD83171001, and RD83451301 from the United States Environmental Protection Agency.

References

Achenbach TM, et al. Child/Adolescent Behavioral and Emotional Problems: Implications of Cross-Informant Correlations for Situational Specificity. Psycholog. Bull. 1987; 101:213–232.

Biedermann S, et al. Transfer of bisphenol A from thermal printer paper to the skin. Anal Bioanal Chem. 2010; 398:571–576. [PubMed: 20623271]

Bradman A, et al. Organophosphate urinary metabolite levels during pregnancy and after delivery in women living in an agricultural community. Environ Health Perspect. 2005; 113:1802–1807. [PubMed: 16330368]

Braun JM, et al. Impact of early-life bisphenol A exposure on behavior and executive function in children. Pediatrics. 2011; 128:873–882. [PubMed: 22025598]

Braun JM, et al. Prenatal bisphenol A exposure and early childhood behavior. Environ Health Perspect. 2009; 117:1945–1952. [PubMed: 20049216]

Calafat AM, et al. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003–2004. Environ Health Perspect. 2008; 116:39–44. [PubMed: 18197297]

Caldwell, B.; Bradley, R. Home observation for measurement of the environment. Little Rock, AR: University of Arkansas; 1984.

Conners, CK. Conner's Rating Scales - Revised (CSR-R) Technical Manual (includes auxilliary scales: CADS-P and CADS-T). North Tonawanda, NY: Multi-Health Systems Inc. (MHS); 2001.

Conners, CK.; Staff, M. Conners' Kiddie Continuous Performance Test (K-CPT): Computer Program for Windows Technical Guide and Software Manual. Toronto, ON: MHS; 2001.

Cox KH, et al. Gestational exposure to bisphenol A and cross-fostering affect behaviors in juvenile mice. Horm Behav. 2010; 58:754–761. [PubMed: 20691692]

Farabollini F, et al. Perinatal exposure to the estrogenic pollutant bisphenol A affects behavior in male and female rats. Pharmacol Biochem Behav. 1999; 64:687–694. [PubMed: 10593191]

Geens T, et al. Are potential sources for human exposure to bisphenol-A overlooked? Int J Hyg Environ Health. 2011; 214:339–347. [PubMed: 21570349]

Ishido M, et al. Bisphenol A causes hyperactivity in the rat concomitantly with impairment of tyrosine hydroxylase immunoreactivity. J Neurosci Res. 2004; 76:423–433. [PubMed: 15079872]

Ishido M, et al. Mesencephalic neurodegeneration in the orally administered bisphenol A-caused hyperactive rats. Toxicol Lett. 2007; 173:66–72. [PubMed: 17689037]

Lubin JH, et al. Epidemiologic evaluation of measurement data in the presence of detection limits. Environ Health Perspect. 2004; 112:1691–1696. [PubMed: 15579415]

Mahalingaiah S, et al. Temporal variability and predictors of urinary bisphenol A concentrations in men and women. Environ Health Perspect. 2008; 116:173–178. [PubMed: 18288314]

Marks AR, et al. Organophosphate Pesticide Exposure and Attention in Young Mexican-American Children: The CHAMACOS Study. Environ Health Perspect. 2010; 118:1768–1774. [PubMed: 21126939]

Maserejian NN, et al. Dental composite restorations and psychosocial function in children. Pediatrics. 2012; 130:e328–e338. [PubMed: 22802599]

Masuo Y, et al. Motor hyperactivity caused by a deficit in dopaminergic neurons and the effects of endocrine disruptors: a study inspired by the physiological roles of PACAP in the brain. Regul Pept. 2004; 123:225–234. [PubMed: 15518916]

Matsuda S, et al. Effects of perinatal exposure to low dose of bisphenol A on anxiety like behavior and dopamine metabolites in brain. Prog Neuropsychopharmacol Biol Psychiatry. 2012; 39:273–279. [PubMed: 22760093]

Miodovnik A, et al. Endocrine disruptors and childhood social impairment. Neurotoxicology. 2011; 32:261–267. [PubMed: 21182865]

Nakagami A, et al. Alterations in male infant behaviors towards its mother by prenatal exposure to bisphenol A in cynomolgus monkeys (Macaca fascicularis) during early suckling period. Psychoneuroendocrinology. 2009; 34:1189–1197. [PubMed: 19345509]

Offord DR, et al. Integrating Data from Multiple Informants. J. Am. Acad. Adolesc. Psychiatry. 1996; 35:1078–1085.

Patisaul HB, Bateman HL. Neonatal exposure to endocrine active compounds or an ERbeta agonist increases adult anxiety and aggression in gonadally intact male rats. Horm Behav. 2008; 53:580–588. [PubMed: 18308321]

Patisaul HB, et al. Neonatal genistein or bisphenol-A exposure alters sexual differentiation of the AVPV. Neurotoxicol Teratol. 2006; 28:111–118. [PubMed: 16427766]

Patisaul HB, et al. Differential disruption of nuclear volume and neuronal phenotype in the preoptic area by neonatal exposure to genistein and bisphenol-A. Neurotoxicology. 2007; 28:1–12. [PubMed: 17109964]

Patisaul HB, Polston EK. Influence of endocrine active compounds on the developing rodent brain. Brain Res Rev. 2008; 57:352–362. [PubMed: 17822772]

Perera F, et al. Prenatal bisphenol a exposure and child behavior in an inner-city cohort. Environ Health Perspect. 2012; 120:1190–1194. [PubMed: 22543054]

Poimenova A, et al. Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol A. Neuroscience. 2010; 167:741–749. [PubMed: 20219646]

Radloff L. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Applied Psycological Measurement. 1977; 1:385–401.

Reynolds, CR.; Kamphaus, RW. BASC-2: Behaviour Assessment System for Children, Second Edition Manual. Circle Pines, MN: AGS Publishing; 2004.

Rosner B. Percentage points for a generalized ESD many outlier procedure. Technometrics. 1983; 25:165–172.

Rubin BS, et al. Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol A. Endocrinology. 2006; 147:3681–3691. [PubMed: 16675520]

Ryan BC, Vandenbergh JG. Developmental exposure to environmental estrogens alters anxiety and spatial memory in female mice. Horm Behav. 2006; 50:85–93. [PubMed: 16540110]

Tian YH, et al. Prenatal and postnatal exposure to bisphenol a induces anxiolytic behaviors and cognitive deficits in mice. Synapse. 2010; 64:432–439. [PubMed: 20169576]

Wolstenholme JT, et al. The role of Bisphenol A in shaping the brain, epigenome and behavior. Horm Behav. 2011; 59:296–305. [PubMed: 21029734]

Xu X, et al. Perinatal bisphenol A affects the behavior and SRC-1 expression of male pups but does not influence on the thyroid hormone receptors and its responsive gene. Neurosci Res. 2007; 58:149–155. [PubMed: 17412439]

Xu X, et al. Sex-specific influence of exposure to bisphenol-A between adolescence and young adulthood on mouse behaviors. Neuropharmacology. 2011; 61:565–573. [PubMed: 21570416]

Ye X, et al. Automated on-line column-switching HPLC-MS/MS method with peak focusing for the determination of nine environmental phenols in urine. Anal Chem. 2005; 77:5407–5413. [PubMed: 16097788]

Ye X, et al. Variability of urinary concentrations of bisphenol A in spot samples, first morning voids, and 24-hour collections. Environ Health Perspect. 2011; 119:983–988. [PubMed: 21406337]

Yolton K, et al. Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. Neurotoxicol Teratol. 2011; 33:558–566. [PubMed: 21854843]

Yu C, et al. Pubertal exposure to bisphenol A disrupts behavior in adult C57BL/6J mice. Environ Toxicol Pharmacol. 2011; 31:88–99. [PubMed: 21787673]

Zhou R, et al. Abnormal synaptic plasticity in basolateral amygdala may account for hyperactivity and attention-deficit in male rat exposed perinatally to low-dose bisphenol-A. Neuropharmacology. 2011; 60:789–798. [PubMed: 21277317]

Highlights

- We measured BPA in urine during pregnancy and from children at five years of age.
- We assessed children's behavior at seven years of age by maternal and teacher report.
- Higher prenatal BPA is associated with depression and anxiety in boys.
- Higher childhood BPA is related to internalizing problems and ADHD in boys and girls.
- Higher childhood BPA is associated with externalizing problems in girls.

Table 1

Geometric mean and standard deviation of urinary BPA concentrations (μg/L) by demographic characteristics of the study population, CHAMACOS Study, Salinas, California (n=292).

		Maternal BPA (pregnancy)	Child BPA (5 years)
	N (%)	GM ± GSD	GM ± GSD
Maternal Race/ethnicity			
Latina	288 (98.6)	1.1 ± 2.2	2.5 ± 3.0
Other	4 (1.4)	2.4 ± 1.4 *	3.5 ± 1.6
Maternal Country of Birth			
United States	36 (12.3)	1.5 ± 2.2	3.1 ± 3.6
Mexico	252 (86.3)	1.1 ± 2.2	2.4 ± 2.9
Other	4 (1.4)	0.8 ± 2.7 *	1.9 ± 4.2
At time of pregnancy			
Time in U.S.			
≤ 1 year	67 (23.0)	1.0 ± 2.1	2.8 ± 3.2
2 – 5 years	66 (22.6)	0.9 ± 2.1	2.3 ± 3.1
6 – 10 years	82 (28.1)	1.3 ± 2.3	2.0 ± 2.4
11+ years	48 (16.4)	1.3 ± 2.3	2.7 ± 2.6
Entire life	29 (9.9)	1.5 ± 2.4 **	3.4 ± 4.0
Maternal Education			
≤ 6th Grade	126 (43.2)	1.1 ± 2.3	2.1 ± 2.6
7 – 12th Grade	103 (35.3)	1.1 ± 2.3	2.7 ± 3.4
≥ High School	63 (21.6)	1.2 ± 1.9	2.9 ± 2.8
Maternal Age (years)			
18 – 24	123 (42.1)	1.1 ± 2.2	2.6 ± 2.9
25 – 29	95 (32.5)	1.1 ± 2.1	2.3 ± 2.9
30 – 34	49 (16.8)	1.1 ± 2.2	2.2 ± 2.7
35 – 45	25 (8.6)	1.3 ± 2.7	2.9 ± 4.3
Marital Status			
Married/Living as married	241 (82.5)	1.1 ± 2.1	2.5 ± 3.4
Not Married	51 (17.5)	1.1 ± 2.6	2.5 ± 2.9
Maternal Smoking			
Yes	12 (4.1)	0.9 ± 2.2	2.5 ± 1.9
No	280 (95.9)	1.1 ± 2.2	2.5 ± 3.0
At time of 7 year behavior assessment			
Household Income			
≤ Poverty	205 (70.2)	1.1 ± 2.2	2.5 ± 3.2
> Poverty	87 (29.8)	1.3 ± 2.3 †	2.5 ± 2.4
HOME Score			
< 15	36 (12.3)	1.2 ± 2.1	2.4 ± 3.1
15 – 18	142 (48.6)	1.1 ± 2.3	2.5 ± 2.9

		Maternal BPA (pregnancy)	Child BPA (5 years)
	N (%)	**GM ± GSD**	**GM ± GSD**
≥ 19	114 (39.0)	1.2 ± 2.2	2.6 ± 3.0
Maternal Depression (CES-D)			
Yes (≥16)	80 (27.5)	1.1 ± 2.3	2.3 ± 3.3
No (<16)	211 (72.5)	1.1 ± 2.2	2.6 ± 2.8
Number of Siblings			
0	94 (32.2)	1.0 ± 2.2	2.6 ± 2.8
1	83 (28.4)	1.1 ± 2.1	2.6 ± 2.9
2	70 (24.0)	1.0 ± 2.0	2.1 ± 3.0
≥3	45 (15.4)	1.7 ± 2.6**	2.6 ± 3.2

† p<0.1;

* p<0.05;

** p<0.01 based on ANOVA.

CES-D = Center for Epidemiologic Studies Depression Scale; GM = geometric mean; GSD = geometric standard deviation.

Table 2

Distributions of Urinary Bisphenol A concentrations in CHAMACOS participants (n=292).

	Percentiles				
Measurement	**25th**	**50th**	**75th**	**Range**	**GM ± GSD**
Maternal BPA (Pregnancy Average)					
Unadjusted BPA (μg/L)	0.7	1.1	1.8	<LOD – 33	1.1 ± 2.2
Specific Gravity Adjusted BPA (μg/L)	0.9	1.2	2.0	<LOD – 27	1.3 ± 2.1
Child BPA (5 Year)					
Unadjusted BPA (μg/L)	1.2	2.3	4.3	<LOD – 442	2.5 ± 3.0
Creatinine Adjusted BPA (μg/g)	2.0	3.2	5.5	<LOD – 350	3.7 ± 2.6

Limit of detection (LOD)=0.4 μg/L; GM=geometric mean; GSD=geometric standard deviation. Maternal samples were collected in 1999–2000 and child samples in 2005–2006.

Table 3

Association of prenatal urinary BPA concentration (log2, specific gravity adjusted) and continuous behavior outcomes at 7 years of age. CHAMACOS Study, Salinas, California.

	Boys		Girls		BPA × Sex
	N	β(9'5% CI)	N	β(95%CI)	p-value
Mother report[a]					
BASC-2					
Internalizing Problems	133	1.8 (0.3,3.3) *	155	0.0 (−1.4,1.3)	0.04
Anxiety scale	133	1.5 (−0.3,3.2) †	155	0.5 (−0.8,1.8)	0.30
Depression scale	135	1.5 (0.0,3.0) *	156	0.1 (−1.2,1.3)	0.10
Somatization scale	133	1.3 (−0.1,2.7) †	155	−0.7 (−2.2,0.8)	0.03
Externalizing Problems	133	0.7 (−1.1,2.5)	155	−0.3 (−1.3,0.7)	0.14
Aggression scale	135	0.5 (−1.2,2.1)	156	0.2 (−0.8,1.1)	0.35
Conduct problems scale	133	1.1 (−0.7,3)	155	−0.9 (−2.1,0.4)	0.02
Hyperactivity scale	133	0.1 (−1.5,1.8)	155	−0.3 (−1.2,0.7)	0.62
Attention scale	133	−0.2 (−1.1,0.8)	155	−0.3 (−1.1,0.4)	0.66
CADS					
Inattention DSM-IV	135	0.1 (−1.3,1.5)	156	−0.5 (−1.5,0.5)	0.59
Hyperactive DSM-IV	135	0.3 (−1.3,1.9)	156	0.0 (−1.1,1.1)	0.83
ADHD DSM-IV	135	0.3 (−1.2,1.8)	156	−0.2 (−1.3,0.8)	0.69
Teacher report[b]					
BASC-2					
Internalizing Problems	114	2.5 (0.7,4.4) **	131	−1.0 (−3.1,1.1)	0.03
Anxiety scale	114	1.9 (0.0,3.7) *	131	−1.7 (−3.7,0.4)	0.01
Depression scale	114	3.2 (1.4,5.1) **	131	−0.2 (−1.8,1.4)	0.01
Somatization scale	114	0.8 (−1.1,2.8)	131	−0.5 (−2.9,1.8)	0.51
Externalizing Problems	114	1.8 (−0.5,4.1)	131	−0.5 (−1.8,0.8)	0.07
Aggression scale	114	2.7 (0.3,5.1) *	131	−0.1 (−1.4,1.1)	0.04
Conduct problems scale	114	1.1 (−0.9,3.1)	131	−0.3 (−1.7,1.1)	0.26
Hyperactivity scale	114	1.1 (−1.3,3.4)	131	−0.9 (−2.2,0.4)	0.11

	Boys		Girls	BPA × Sex
	N	β(9'5% CI)	N	β(95%CI)	p-value
Attention scale	114	−0.1 (−1.4,1.2)	131	−0.4 (−1.3,0.5)	0.62
CADS					
Inattention DSM-IV	114	0.3 (−1.5,2.2)	130	−0.6 (−1.9,0.7)	0.38
Hyperactive DSM-IV	114	1.4 (−0.6,3.5)	130	−1.6 (−3.3,0.2) †	0.03
ADHD DSM-IV	113	0.8 (−1.2,2.7)	127	−1.2 (−2.9,0.4)	0.13

[a] Adjusted for mother's country of birth, maternal education, marital status, maternal language of interview, child's exact age, HOME score, household income, number of siblings, maternal depression at 7 years, child's BPA at 5 years, and maternal DAP metabolite levels during pregnancy.

[b] Adjusted for mother's country of birth, maternal education, marital status, child's age, HOME score, household income, number of siblings, child's BPA at 5 years and maternal DAP metabolite levels during pregnancy.

† p<0.1;

* p<0.05;

** p<0.01

Table 4

Association of childhood urinary BPA concentration (log_2, creatinine-adjusted) and continuous behavior outcomes at 7 years of age. CHAMACOS Study, Salinas, California.

	Boys		Girls		BPA × Sex
	N	β(95% CI)	N	β(95% CI)	p-value
Mother report[a]					
BASC-2					
Internalizing Problems	133	−0.3 (−1.2,0.7)	155	0.3 (−0.9,1.5)	0.34
Anxiety scale	133	0.3 (−0.9,1.4)	155	−0.7 (−1.9,0.5)	0.35
Depression scale	135	−0.4 (−1.4,0.6)	156	0.7 (−0.4,1.8)	0.07
Somatization scale	133	−0.4 (−1.3,0.5)	155	0.7 (−0.6,2.1)	0.13
Externalizing Problems	133	−0.3 (−1.4,0.9)	155	1.2 (0.3,2.1) *	0.05
Aggression scale	135	−0.2 (−1.3,0.8)	156	0.7 (−0.1,1.6) †	0.13
Conduct problems scale	133	−0.3 (−1.5,0.9)	155	1.8 (0.8,2.9) **	0.02
Hyperactivity scale	133	−0.2 (−1.2,0.9)	155	0.6 (−0.3,1.4)	0.30
Attention scale	133	0.5 (−0.2,1.1)	155	0.9 (0.2,1.6) **	0.31
CADS					
Inattention DSM-IV	135	0.0 (−0.9,0.9)	156	1.3 (0.4,2.2) **	0.03
Hyperactive DSM-IV	135	−0.3 (−1.3,0.8)	156	1.1 (0.1,2.0) *	0.05
ADHD DSM-IV	135	−0.2 (−1.1,0.8)	156	1.3 (0.3,2.3) **	0.03
Teacher report[b]					
BASC-2					
Internalizing Problems	114	1.8 (0.4,3.1) *	131	1.8 (0.1,3.6) *	0.92
Anxiety scale	114	1.6 (0.3,3.0) *	131	1.5 (−0.3,3.2) †	0.99
Depression scale	114	1.2 (−0.1,2.5) †	131	1.4 (0.1,2.8) *	0.97
Somatization scale	114	1.2 (−0.2,2.7) †	131	1.3 (−0.7,3.3)	0.85
Externalizing Problems	114	0.5 (−1.2,2.2)	131	1.0 (−0.1,2.0) †	0.72
Aggression scale	114	0.4 (−1.4,2.1)	131	0.9 (−0.2,1.9)	0.77
Conduct problems scale	114	0.5 (−0.9,2.0)	131	0.4 (−0.8,1.6)	0.84

Environ Res. Author manuscript; available in PMC 2014 October 01.

	Boys		Girls		BPA × Sex
	N	β(95% CI)	N	β(95% CI)	p-value
Hyperactivity scale	114	0.6 (−1.1,2.3)	131	1.4 (0.4,2.5) *	0.48
Attention scale	114	1.2 (0.2,2.2) *	131	0.6 (−0.2,1.3)	0.39
CADS					
Inattention DSM-IV	114	1.7 (0.3,3.0) *	130	1.0 (−0.1,2.0) †	0.40
Hyperactive DSM-IV	114	0.4 (−1.1,1.8)	130	1.7 (0.3,3.2) *	0.24
ADHD DSM-IV	113	1.1 (−0.3,2.4)	127	1.7 (0.3,3.1) *	0.58

[a] Adjusted for mother's country of birth, maternal education, marital status, maternal language of interview, child's exact age, HOME score, household income, number of siblings, maternal depression at 7 years, child's BPA at 5 years, and maternal DAP metabolite levels during pregnancy.

[b] Adjusted for mother's country of birth, maternal education, marital status, child's age, HOME score, household income, number of siblings, maternal BPA and DAP metabolite levels during pregnancy.

† p<0.1;

* p<0.05;

** p<0.01

Table 5

Comparison of published studies of BPA and childhood behavior.

	Prenatal BPA		Childhood BPA	
	Boys	**Girls**	**Boys**	**Girls**
Braun et al Exposure: Urinary BPA Outcome: BASC at 2–3 years	↓ hyperactivity	↑ anxiety ↑ depression ↑ hyperactivity ↑ externalizing	No associations	No associations
Perera et al Exposure: Urinary BPA Outcome: CBCL at 3–5 years	↑ aggression ↑ emotional reactivity	↓ anxiety ↓ aggression	No associations	No associations
Harley et al (present study) Exposure: Urinary BPA Outcome: BASC, CADS at 7 years	↑ anxiety ↑ depression ↑ somatization ↑ aggression ↑ Internalizing	No associations	↑ anxiety ↑ depression ↑ inattention	↑ anxiety ↑ depression ↑ ADHD ↑ externalizing ↑ conduct problems
Maserejian et al Exposure: Dental composite (surface-yrs) Outcome: BASC, CBLC At 10–16 years			↑ anxiety ↑ depression ↑ emotional problems ↑ maladjustment	