HHS Public Access

Author manuscript

Reprod Toxicol. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Reprod Toxicol. 2015 January ; 51: 7–13. doi:10.1016/j.reprotox.2014.11.003.

Urinary Bisphenol A and Semen Quality, The LIFE Study

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Abstract

Bisphenol A (BPA), a high-production volume industrial chemical found in several consumer products, has been negatively associated with sperm quality. This study aimed to estimate the association between BPA and 35 measures of semen quality among reproductive aged men recruited from 16 counties in Michigan and Texas, 2005–2009. Of 501 enrolled males, 418 (83.4%) provided a urine sample and at least one semen sample. Linear and logistic regression models assessed the association between urinary BPA levels and individual semen quality endpoints. Generalized Estimating Equations were used to account for repeated measures of semen quality and adjusted models accounted for 11 *a priori* covariates. Geometric mean total urinary BPA concentration among participants was 0.55 ng/mL (95% CI 0.49–0.63). A negative relation between BPA and DNA fragmentation was the sole significant finding in adjusted linear regression (β=−0.0544, p=0.035) and suggestive of less sperm DNA damage.

Keywords

Bisphenol A; DNA Fragmentation; Endocrine Disruptors; Fecundity; Fertility; Semen; Sperm; Sperm Chromatin Structure Assay

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1. Introduction

Bisphenol A (BPA) is a high production industrial chemical, used mainly in epoxy resins and polycarbonate plastics [1]. Five to six million pounds of BPA are produced annually for use in consumer products such as water bottles, baby bottles, eye glasses frames, dental sealants, thermal receipts, medical equipment, flooring, reusable food and drink containers, CDs, toys, impact-resistant safety equipment and as a liner in water supply pipes and food cans [2,3,4]. BPA can leach into water or food products at high temperatures or in acidic or alkaline environments [3], and may also leach from certain products during normal use [4]. As such, the main route of human exposure is thought to be through dietary ingestion [1,2].

Following oral exposure, the body readily absorbs BPA and the chemical is quickly metabolized by the liver into two different forms [1,2,3]. The majority of BPA is metabolized by glucuronidation into the conjugated compound, bisphenol A glucuronide [1]. The conjugated form is water-soluble and, as a result, is less biologically active and quickly excreted via urine [1,2,3]. The unconjugated BPA (or “free” BPA) comprises up to 12 percent of total BPA levels in blood and is thought to be the active form [1,3]. However, unconjugated BPA levels are low among the general population and are also difficult to detect, so biomonitoring and other epidemiological studies typically measure total BPA concentrations (i.e., sum of conjugated and unconjugated forms) [1,3].

BPA exposure is widespread among the U.S. general population. Over 90 percent of the participants in the 2003–2004 and 2009–2010 National Health and Nutrition Examination Survey (NHANES) subsets had detectable total urinary BPA levels, though creatinine adjusted urinary concentrations were lower in males than females [2,3,5]. In addition to urine, BPA has been detected in a number of other biological matrices including serum, breast milk, follicular fluid, amniotic fluid, placental tissue and umbilical cord serum [1,3,4]. The high prevalence of exposure to BPA has fueled concern about BPA’s ability to negatively impact human development and reproduction.

BPA has demonstrated an ability to disrupt hormone-signaling systems in laboratory animals [1,6,7,8]. These endocrine disrupting effects have been observed at both high- and low-dose concentrations that are relevant to human exposures [1]. Male rodents exposed to low levels of BPA displayed several reproductive and developmental impacts including decreased serum testosterone levels and sperm quality [9]. In epidemiological studies, BPA has demonstrated an association with follicle stimulating hormone, inhibin B, estradiol: testosterone levels, and sexual function among males [10,11,12,13].

To our knowledge and despite ubiquitous exposure, only five studies have been published regarding the association of BPA exposure and human semen quality. Li et al. identified an inverse association between total urinary BPA levels and semen concentration, total sperm count, sperm vitality and sperm motility among 218 Chinese factory workers; the effects remained statistically significant when analyses were restricted to those workers who were not occupationally exposed to BPA [14]. Furthermore, two studies conducted among male partners of couples seeking treatment at infertility clinics corroborated these findings [15,16]. In a sample of 190 men recruited from Massachusetts General Hospital’s Vincent

Andrology Laboratory, Meeker and colleagues identified an inverse relationship between total urinary BPA concentrations and semen concentration, sperm motility, and sperm morphology [15]. Total urinary BPA levels were also associated with decreased sperm count, concentration, and vitality among 149 male partners recruited from a Slovenian university hospital infertility clinic [16]. Moreover, Lassen et al. observed a reduced percentage of progressively motile sperm among young men from the Danish general population in the highest quartile of total urinary BPA [17]. A study of 375 male partners of pregnant women failed to find an association between total urinary BPA levels and semen quality [18]. The Longitudinal Investigation of Fertility and the Environment (LIFE) Study aims to further contribute to this growing body of knowledge by exploring the impact of total urinary BPA concentrations on 35 semen quality endpoints among men recruited from population rather than clinical or occupational settings. This study context is important for exploring whether exposure is associated with impaired fertility in the general population irrespective of medical care seeking behaviors or occupational exposures.

2. Materials and methods

2.1 Study Population

Male participants were recruited as a part of the LIFE Study, which is a prospective cohort study with preconception enrollment of couples who discontinued contraception to become pregnant [19]. State-specific sampling frameworks were utilized to recruit participants between 2005–2009 from four counties in Michigan and twelve counties in Texas. Couples were eligible for enrollment if they met the following inclusion criteria: 1) women aged 18–40 and men aged 18+ years; 2) married or in a committed relationship; 3) women's menstrual cycles between 21 and 42 days consistent with female's use of the fertility monitor; 4) no injectable contraceptives within the past year due to their potential long lasting effects on fecundity; 5) planning a pregnancy and off contraception for less than 2 months; 6) no sterilization procedures or physician diagnosed infertility; and 7) and an ability to communicate in English or Spanish.

2.2 Data and Biospecimen Collection

A research nurse and an interviewer traveled to the couples' homes to conduct baseline in-person interviews and to collect information on various lifestyle factors and reproductive history, obtain baseline blood and urine samples, and to instruct couples for collecting further biospecimens (i.e., saliva, semen, urine). Initial urine samples were collected during the baseline visit and were used to measure total BPA. Cotinine concentrations were quantified in serum. Following two days of abstinence, male participants collected a baseline semen sample and a second sample approximately one month later. Samples were collected via masturbation without the use of lubricant. To maintain and insure sperm integrity, participants were given a home collection kit that included an insulated shipping container (Hamilton Research, Beverly, MA, USA), a glass specimen jar with an attached temperature data logger (I-Button, Maxim Integrated), a sperm migration straw filled with hyaluronic acid and plugged at one end, and packing materials (Vitrotubes #3520, VitroCom) [20]. Samples were shipped overnight and analyzed the following day. Full

Institutional Review Board approval was obtained for all collaborating sites, and all study participants gave informed consent before any data collection.

2.3 Total BPA Analysis

BPA analysis was performed at the Wadsworth Center within the New York State Department of Health using published procedures [21]. High-performance liquid chromatography (HPLC) coupled with API 2000 electrospray triple-quadrupole mass spectrometry (ESI-MS/MS) was utilized to measure urinary levels of total BPA (ng/mL) after enzymatic deconjugation. Laboratory methods were validated by testing spiked samples for analyte recovery. The limit of quantification was 0.05 ng/mL. Several quality assurance/quality control (QA/QC) protocols were followed throughout the analysis, which include procedural blanks, matrix spikes, and spiking of labeled internal standard in each of the samples analyzed. Trace levels of BPA found in procedural blanks were subtracted from sample values. Quantification was by isotope dilution method. The laboratory participated in proficiency testing programs conducted by the Centers for Disease Control and Prevention to validate the analysis of BPA in urine; the results for BPA were within +/−15% of the actual value.

Liquid chromatography-isotope dilution tandem mass spectrometry was used to assess cotinine concentrations (ng/mL) in 1 mL of serum [22], while levels of creatinine (mg/dL) in 0.15 mL of urine were assessed by a Roche/Hitachi Model 912 clinical analyzer (Dallas, TX) and the Creatinine Plus Assay.

2.4 Andrology Analysis

After being shipped via pre-paid overnight shipping, semen samples were received the next day at the National Institute for Occupational Safely and Health's andrology laboratory where all samples were inspected for turbidity, color, liquefaction, and volume. Temperature was assessed by inspecting data from the thermometer (Maxim Integrated, San Jose, CA, USA) attached to the semen collection jar. All samples were found to be within range and were used for analysis. Subsequently, the HTM-IVOS (Hamilton Thorne) computer assisted semen analysis system (CASA) was used to determine sperm motility after an aliquot of sample was placed in a 20-μm-deep chamber slide (Leja, Luzemestraat, Netherlands). The IVOS system and INDENT stain were used to assess sperm concentration. Microscope slides were prepared to measure sperm morphometry and morphology. The IVOS METRIX system was used to carry out sperm morphometry analyses. Evaluations of sperm morphology were done in a contracted laboratory using the prepared slides and included both the traditional with differential classification, as well as the strict morphology assessments. For the sperm chromatin structure assay (SCSA) analysis, an aliquot of whole semen was diluted in Tris NaCl EDTA (TNE) buffer with glycerol and frozen. Hypo-osmotic swelling was used to determine sperm viability. To assess the distance traveled (mm) by the vanguard sperm, the sperm migration straw was removed from the semen in the glass specimen jar and examined under the microscope. Further details have been published elsewhere [19].

Thirty-five endpoints of semen quality were assessed in the initial semen sample, including 5 general parameters (semen volume (mL), straw distance (mm), sperm concentration ($x10^6$/mL), total sperm count ($x10^6$/ejaculate), and hypo-osmotic swelling (%)), 8 24-hour motility measures (average path velocity (μm/sec), straight line velocity (μm/sec), curvilinear velocity (μm/sec), amplitude head displacement (μm), beat cross frequency (Hz), straightness (%), linearity (%), and percent motility (%)), 6 sperm head measures (length (μm), area (μm^2), width (μm), perimeter (μm), elongation factor (%), and acrosome area of head (%)), 14 morphology measures (strict criteria (%), traditional normal (%), amorphous (%), round (%), pyriform (%), bicephalic (%), taper (%), megalo head (%), micro head (%), neck and midpiece abnormalities (%), coiled tail (%), other tail abnormalities (%), cytoplasmic droplet (%), and immature sperm (n)), and 2 SCSA measures (DNA fragmentation index (%) and high DNA stainability (%)). An abbreviated analysis was performed on the second sample and included 4 of the 5 general parameters (semen volume (mL), sperm concentration ($x10^6$/mL), total sperm count ($x10^6$/ejaculate), and hypo-osmotic swelling (%)), 8 24-hour motility measures (average path velocity (μm/sec), straight line velocity (μm/sec), curvilinear velocity (μm/sec), amplitude head displacement (μm), beat cross frequency (Hz), straightness (%), linearity (%), and percent motility (%)), and 6 sperm head measures (length (μm), area (μm^2), width (μm), perimeter (μm), elongation factor (%), and acrosome area of head (%). Of note, some endpoints are derived from others and are not independent, *per se*. Specifically, sperm concentration/ml semen is determined in an aliquot of diluted semen using the hemacytometer and then this is multiplied by the sample volume to get total sperm in the sample. Sperm motility parameters are derived mathematically from computer generated sperm track, while sperm head area, perimeter, and elongation factor are functions of sperm head length and width.

2.5 Statistical Analyses

A number of descriptive analyses were performed to evaluate our study population. Specifically, Chi-square and nonparametric Wilcoxon tests were used to compare the percent distribution of categorical and continuous socio-demographic characteristics, respectively, by whether or not the male provided a semen sample. The same tests were used to assess the demographic characteristics of men by the provision or not of urine samples for BPA quantification. Summary statistics were also calculated to determine the distribution of total urinary BPA concentration, urinary creatinine concentration, and semen quality parameters.

In the analytical phase, linear and logistic regression models were run to determine the association between urinary BPA and individual semen quality parameters. Linear regression models were run first and estimated the effect of urinary BPA concentration on individual, Box-Cox transformed semen quality endpoints, when measured as continuous variables. Logistic regression models were also utilized to enable comparability with the World Health Organization's semen quality reference values with the exception of motility given our reliance on next day analysis [23]. Seven untransformed endpoints (semen volume (mL), sperm concentration ($x10^6$/mL), total sperm count ($x10^6$/ejaculate), hypo-osmotic swelling (%), strict criteria (%), traditional normal (%), and DNA fragmentation index (%)) were dichotomized as below or at/above the respective WHO reference value.

Unadjusted and adjusted analyses in both sets of models used Generalized Estimating Equations to account for repeated measures of semen quality for endpoints measured in both samples. Regression models accounted for *a priori* covariates as identified from the existing literature: abstinence time (days), age (years), alcohol consumption (frequency per month) upon enrollment, body mass index (BMI; weight in kg/height in m^2) [24], urinary creatinine (mg/dL), educational attainment (<High school, High school grad, Some college, College), household income (US dollars), previously fathered pregnancy (number of pregnancies), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), serum cotinine (ng/mL), and study site (Texas/Michigan). BPA concentrations were natural log-transformed and semen quality endpoints were Box-Cox transformed (linear regression only) to approximate a normal distribution. Separate models were run for each semen endpoint and statistical significance was set at $p < 0.05$ without adjustment for multiple comparisons consistent with this exploratory analysis. All analyses were performed in SAS version 9.3.

3. Results

This study cohort comprised mostly non-Hispanic White (78.6%) males, who were mostly overweight (83.2%) and college-educated (62.5%). The average age among participating males was 31.7±4.9 years and mean BMI was 29.5±6.8 kg/m^2. Of the 501 men enrolled in the LIFE Study, 418 (83.4%) provided a urine sample and at least one semen sample. Table 1 indicates that as compared to men who did not provide at least one sample, men who did generally had higher household income ($p<0.01$) and educational attainment ($p=0.035$), were more likely to be White ($p<0.01$), and were more likely to be enrolled at the Michigan study site ($p<0.01$). BPA concentrations did not differ significantly between these two groups (data not shown). All semen quality parameters were similar between the first and second samples with the exception of the percentage of hypo-osmotic swollen sperm, which was higher in the first semen sample ($p<0.04$, data not shown). When considering urine samples, men who provided sufficient volume for BPA quantification were more likely to be enrolled at the Texas location than men who did not (data not shown). The unadjusted geometric mean total urinary BPA concentration in this cohort was 0.55 ng/mL (95% CI 0.49–0.63). No difference was observed in mean concentration by provision of a semen sample or after creatinine adjustment.

Among male LIFE Study participants, urinary BPA concentration was associated with only one semen quality parameter when modeled as continuous outcomes (Table 2). Specifically, increasing BPA concentration was observed to be associated with lower DNA fragmentation in both the unadjusted ($\beta= -0.0649$, $p=0.002$) and adjusted ($\beta= -0.0544$, $p=0.035$) linear regression models. When modeling BPA in relation to select WHO dichotomized semen quality endpoints, no findings achieved statistical significance (Table 3). Total urinary BPA was not associated with any other semen quality endpoints

4. Discussion

Our analyses suggest that total urinary BPA concentration in men recruited from the general population of two states is associated with less sperm DNA fragmentation but not other parameters of semen quality. When attempting to assess the fertility implications of semen

quality endpoints, we categorized various endpoints (with the exception of motility) at the fifth percentile, given our reliance on next day analysis, per the WHO criteria and observed no significant associations. Of particular note is the relatively low distribution of BPA concentrations measured in our cohort of males, which may reflect our population-based rather than clinic or workplace based sampling of study participants.

Interpretation of our findings in the context of available literature is difficult, as there is a dearth of epidemiologic data on the association of BPA and semen quality, in general, and DNA fragmentation, specifically. Further interpretation of this finding is challenging in light of past literature reporting positive associations. In a study of male rats, BPA exposure was associated with a significant increase in four measures of sperm DNA damage [25]. Finally, in a study of human semen quality, Meeker et al. observed a positive association between BPA and sperm DNA assessed with the COMET assay [15].

Another explanation for the inconsistency in observed signal direction between the LIFE Study and other published studies might be the relatively lower BPA concentrations in the former study. Men in the LIFE Study had a lower geometric mean BPA concentration (0.55 ng/mL) than men participating in the NHANES Survey in 2003–2004 (2.92 ng/mL; 95% CI 2.63–3.24) [2], and also lower than among men seeking infertility treatment (1.4 ng/mL) for whom DNA damage was observed to be associated with BPA [15]. Further, the total urinary BPA geometric mean concentration among male LIFE Study participants was lower than that observed in three other studies. Specifically, Knez et al. [16] and Mendiola et al. [18] reported geometric means (5th–95th percentiles) of 1.55 ng/mL (0.3–6.68 ng/mL) among men in Slovenia, and 1.50 ng/mL (<LOD-6.5) among men in Massachusetts, respectively, while Lassen et al. [17] reported a median (5th–95th percentile) unadjusted total urinary BPA concentration of 3.25 ng/mL (0.59–14.89 ng/mL) among Danish men.

Our findings do offer new insights regarding BPA and semen quality, particularly the lack of observed detrimental associations with semen quality when utilizing participants from the general population rather than from clinical or occupational settings care. This may explain our lower urinary concentrations relative to previous studies and, as such, is informative about lower concentrations relative to semen quality. If exposure is associated with fecundity impairments, men seeking care may have higher exposures than men recruited using nonclinical sampling frameworks. A strength of our study is the high percentage of participating men and the use of two semen samples, an inclusive investigation of a spectrum of semen quality endpoints, and reliance on the Sperm Chromatin Structure Assay (SCSA). The SCSA is reported to be a highly sensitive and reliable measure of sperm DNA integrity [26]. The relative incidence of abnormal sperm chromatin structures has been shown to be predictive of human fertility potential [27], even when other measures of semen quality are unimpaired [28, 29, 30]. SCSA has been used to assess the influence of environmental chemicals in previous epidemiological studies [31, 32, 33, 34, 35], but this work is the first to consider BPA.

Still, important limitations must be kept in mind when interpreting the results. First, we relied upon a single spot urine sample for assessing BPA exposure. Though no evidence is available regarding long-term average exposures, recent evidence suggests spot samples

yield a suitable estimate of average daily [36] and weekly [37] exposures. In a sample of eight CDC employees (4 male, 4 female) examined for one week, it was found that first morning and 24-hour voids had high between-day variance in BPA concentration, while spot urine samples had high within-day but relatively low between-day variance [36]. Moreover, in a larger study comprising 217 urine samples from 87 male and female patients at an infertility center, Mahalingaiah and colleagues found that a single urine sample correctly classified participants into the highest BPA exposure tertile with sensitivity and specificity equal to 64 and 76 percent, respectively [38]. Men in this study had a total urinary BPA geometric mean concentration of 1.62 ng/mL, whereas men in the LIFE Study had a geometric mean concentration of 0.55 ng/mL. The extent to which these findings are applicable to longer time intervals such as in the LIFE Study remains to be established. In sum, it is not clear whether a single spot urine sample accurately characterized male LIFE Study participants' BPA exposure during the spermatogenesis window. However, any bias resulting from such exposure misclassification would likely be non-differential resulting in an underestimation of the true association.

Another limitation is our use of next-day analyses to evaluate semen quality, which may have hindered the assessment of time-sensitive parameters such as motility and viability endpoints. Importantly, however, at-home specimen collection has been employed successfully in a previous clinical assessment of environmental factors and semen quality [39]. Luben et al. observed no statistical difference between samples that were assessed within 24-hours versus 1.5 hours in terms of non-motility semen quality endpoints including DNA fragmentation [39]. In light of our reliance on 24-hour motility assessment, an estimate of sperm motility was obtained at the time of specimen collection by placing a migration straw in the specimen after collection. Although next-day semen quality analyses are suitable for epidemiological research, our results are not directly comparable with clinical assessments. Also, we cannot rule out residual confounding or a chance finding in light of the number of comparisons made in this exploratory analysis.

As stated above, BPA and its conjugates have been detected in nearly 93 percent of NHANES participants older than 6 years old [5]. In light of this widespread exposure and concerns over declining human fecundity and semen quality more specifically [40], our study endeavored to reveal possible impacts of BPA on decrements in male fecundity, as measured by semen quality. At the relatively low urinary concentrations of BPA among male LIFE Study participants only a protective effect on DNA fragmentation was observed, though possible mechanisms await further investigation. Among this general population cohort, BPA was not associated with adverse effects on any measure of semen quality.

Conclusion

This exploratory analysis assessing a cohort of men recruited from the general population did not find evidence in support of an adverse relation between total urinary BPA and semen quality even when assessing numerous endpoints. However, reliance on a single spot urine may not have adequately captured BPA exposure during the relevant window for spermatogenesis.

Acknowledgments

This work was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (contracts #N01-HD-3-3355, N01-HD-3-3356, and N01-HD-3-3358). Semen samples were analyzed under a Memorandum of Understanding with NICHD by the Reproductive Health Assessment Team, Biomonitoring and Health Assessments Branch, National Institute for Occupational Safety and Health.

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Highlights

- 501 men were recruited of which 83% provided urine and semen samples for analysis
- Geometric mean total urinary BPA concentration was 0.55 ng/mL (95% CI 0.49–0.63)
- Only one significant association was observed between urinary BPA concentrations and DNA fragmentation ($\beta=-0.0544$, $p=0.035$)
- No evidence that BPA diminishes semen quality in this cohort

Table 1

Percent distribution of socio-demographic characteristics by provision of semen sample, LIFE Study (n=501)

Characteristic	Provided semen sample (n=473)	Did not provide semen sample (n=28)	p-value[a]
	n (%)	n (%)	
Abstinence time (# days)			
<2	2 (0.4)	NA	NA
2 to 7	424 (89.6)	NA	
>7	34 (7.2)	NA	
Missing	13 (2.8)	NA	
Mean (±SD)	4.01 (4.5)	NA	
Age (years)			
<25	16 (3.4)	3 (10.7)	0.18
25–29	151 (31.9)	6 (21.4)	
30–34	176 (37.2)	10 (35.7)	
35+	130 (27.5)	9 (32.1)	
Mean (±SD)	31.8 (4.9)	31.7 (5.9)	
Alcohol consumption			
Once a month or less	65 (13.7)	4 (16.7)	0.55
Two or three days a month	75 (15.9)	5 (17.9)	
Once a week	105 (22.2)	3 (10.7)	
Two or three times a week	122 (25.8)	7 (25.0)	
Four to six times a week or more	37 (7.8)	3 (10.7)	
Missing	69 (14.6)	4 (14.3)	
Body Mass Index			
<18.5 (underweight)	2 (0.4)	0 (0.0)	0.77
18.5–24.9 (normal weight)	75 (15.9)	3 (10.7)	
25–29.9 (overweight)	188 (39.8)	14 (50.0)	
≥30 (obese)	184 (38.9)	11 (39.3)	
Missing	24 (5.1)	0 (0.0)	
Mean (±SD)	29.5 (5.0)	29.2 (4.0)	
Education			

Characteristic	Provided semen sample (n=473)	Did not provide semen sample (n=28)	p-value[a]
	n (%)	n (%)	
High school grad/GED[c] or less	38 (8.0)	6 (21.4)	0.04
Some college/technical school	133 (28.1)	9 (32.0)	
College graduate or higher	298 (63.0)	12 (42.9)	
Missing	4 (0.9)	1 (3.6)	
Household income			
<$29,999	20 (4.2)	6 (21.5)	<0.01
$30,000 – $49,000	60 (12.7)	3 (10.7)	
$50,000 – $69,999	66 (14.0)	2 (7.1)	
$70,000+	44 (9.5)	3 (10.7)	
Previously fathered (#)			
0	246 (52.0)	13 (46.4)	0.83
1	159 (33.6)	10 (35.7)	
2	50 (10.6)	4 (14.3)	
3	15 (3.2)	0 (0.0)	
4	1 (0.2)	0 (0.0)	
missing	2 (0.4)	1 (3.6)	
Race/ethnicity			
Hispanic	38 (8.0)	7 (25.0)	<0.01
Non-Hispanic Black	20 (4.2)	3 (10.7)	
Non-Hispanic White	381 (80.5)	13 (46.4)	
Other	34 (7.2)	5 (17.9)	
Site			
Michigan	98 (20.7)	0 (0.0)	<0.01
Texas	375 (79.3)	28 (100.0)	
Geometric mean (95% confidence interval)			
Urinary BPA (ng/mL)	0.55 (0.48, 0.62)	0.67 (0.36, 1.26)	0.48
Creatinine adjusted urinary BPA (μg/g)	0.51 (0.46, 0.58)	0.56 (0.31, 0.99)	0.68
Serum cotinine (ng/mL)[d]	0.04 (0.04–0.06)	0.09 (0.03–0.24)	0.07
Creatinine (mg/dL)[d]	6.55 (6.45–6.66)	6.66 (6.23–7.12)	0.54

[a] Chi-squared tests were used in the two-way comparisons of categorical variables between men who provided a semen sample and men who did not. Nonparametric Wilcoxon tests were used in the two-way comparisons of continuous variables between men who provided a semen sample and men who did not. P-values refer to differences in n (%) and geometric means (GM) and 95% Confidence Interval (CI)

[b] NA= not applicable - no semen sample

[c] GED= General Education Development Exam

[d] Natural logarithm-transformed and standardized

Reprod Toxicol. Author manuscript; available in PMC 2016 January 01.

Table 2

Linear regression coefficients (standard error) for change in semen quality endpoints by total urinary BPA concentration, LIFE Study

Semen quality endpoint[a,b]	Unadjusted model[c]		Adjusted model[c,d]	
	BPA concentration β (SE)	p-value	BPA concentration β (SE)	p-value
General characteristics				
Volume (mL)	0.01 (0.03)	0.85	0.06 (0.03)	0.07
Straw distance (mm)	0.01 (0.04)	0.71	0.03 (0.04)	0.52
Sperm concentration (x10^6/mL)	−0.02 (0.10)	0.83	−0.07 (0.12)	0.56
Total sperm count (x 10^6/ejaculate)	0.02 (0.15)	0.91	0.11 (0.18)	0.54
Hypo-osmotic swollen (%)	0.43 (0.38)	0.26	−0.42 (0.48)	0.38
Sperm motility				
Average path velocity (μm/sec)	0.11 (0.31)	0.73	−0.09 (0.38)	0.81
Straight line velocity (μm/sec)	−0.03 (0.30)	0.93	−0.06 (0.36)	0.87
Curvilinear velocity (μm/sec)	0.08 (0.54)	0.88	−0.22 (0.67)	0.74
Amplitude head displacement (μm)	−0.00 (0.04)	0.92	−0.06 (0.05)	0.23
Beat cross frequency (Hz)	−0.32 (0.18)	0.08	0.06 (0.23)	0.79
Straightness (%)	−0.27 (0.29)	0.35	0.04 (0.38)	0.91
Linearity (%)	−0.19 (0.29)	0.52	0.00 (0.37)	0.99
Percent motility (%)	−0.01 (0.08)	0.93	−0.04 (0.10)	0.65
Sperm head measurements				
Length (μm)	0.00 (0.00)	0.17	0.00 (0.00)	0.17
Area (μm^2)	0.02 (0.03)	0.50	0.07 (0.04)	0.10
Width (μm)	−0.01 (0.01)	0.46	0.01 (0.01)	0.43
Perimeter (μm)	0.02 (0.02)	0.26	0.04 (0.02)	0.10
Elongation factor (%)	−0.29 (0.20)	0.13	−0.11 (0.25)	0.66
Acrosome area of head (%)	0.09 (0.18)	0.64	0.19 (0.22)	0.40
Morphology				
Strict criteria (%)	−0.04 (0.21)	0.84	0.28 (0.27)	0.31
Traditional normal (%)	0.09 (0.62)	0.89	1.22 (0.78)	0.12
Amorphous (%)	0.04 (0.05)	0.40	0.02 (0.07)	0.73
Round (%)	0.03 (0.04)	0.15	0.08 (0.05)	0.14

Semen quality endpoint[a,b]	Unadjusted model[c]		Adjusted model[c,d]	
	BPA concentration β (SE)	p-value	BPA concentration β (SE)	p-value
Pyriform (%)	−0.02 (0.05)	0.77	−0.03 (0.07)	0.62
Bicephalic (%)	−0.03 (0.05)	0.58	−0.05 (0.06)	0.43
Taper (%)	0.03 (0.05)	0.50	−0.02 (0.06)	0.73
Megalo head (%)	0.09 (0.04)	0.81	0.06 (0.04)	0.15
Micro head (%)	−0.01 (0.04)	0.84	−0.04 (0.04)	0.35
Neck and midpiece abnormalities (%)	−0.00 (0.01)	0.85	−0.01 (0.02)	0.73
Coiled tail (%)	−0.03 (0.02)	0.25	−0.05 (0.03)	0.09
Other tail abnormalities (%)	−0.05 (0.04)	0.18	−0.08 (0.04)	0.07
Cytoplasmic droplet (%)	−0.06 (0.05)	0.29	−0.13 (0.07)	0.05
Immature sperm (n)	0.00 (0.05)	0.92	0.00 (0.07)	0.95
Sperm chromatin structure assay				
DNA fragmentation index	−0.07 (0.02)	0.00	−0.05 (0.03)	0.04
High DNA stainability	0.00 (0.02)	0.98	0.03 (0.03)	0.28

NOTE: All beta coefficients and standard errors were rounded to two decimal places.

[a] All semen quality endpoints were transformed using the Box-Cox transformation.

[b] Separate models were run for each individual endpoint.

[c] When modeling the association between BPA and semen quality endpoints that were assessed in both semen samples, the association between first and second samples was accounted for by using Generalized Estimating Equations (GEE).

[d] Multivariate linear regression models were adjusted for age (continuous), abstinence time (continuous), alcohol consumption (categorical), body mass index (continuous), creatinine (continuous), education (categorical), income (categorical), previously fathered pregnancy (continuous), serum cotinine (continuous), study site (categorical), and race/ethnicity (categorical).

Table 3

Logistic regression coefficients (standard error) for change in dichotomized semen quality parameter by total urinary BPA concentration, LIFE Study

Semen quality endpoint[a,b]	Unadjusted model		Adjusted model[e]	
	BPA concentration β (SE)	p-value	BPA concentration β (SE)	p-value
General characteristics				
Volume (mL)[d]	0.03 (0.12)	0.80	−0.42 (0.24)	0.08
Sperm concentration (x10^6/mL)[d]	−0.23 (0.15)	0.13	−0.25 (0.23)	0.27
Total sperm count (x10^6/ejaculate)[d]	−0.04 (0.13)	0.77	−0.28 (0.24)	0.25
Hypo-osmotic swollen (%)[d]	−0.07 (0.10)	0.50	0.03 (0.14)	0.83
Morphology				
Strict criteria (%)[c]	0.10 (0.22)	0.67	−1.10 (0.75)	0.14
Traditional normal (%)[c]	0.01 (0.10)	0.90	−0.19 (0.15)	0.20
Sperm chromatin structure assay				
DNA fragmentation index (%)[d]	0.49 (0.31)	0.11	0.76 (0.58)	0.19

[a] Semen quality endpoints are restricted to those with World Health Organization reference values.[23]

[b] Semen quality endpoints are in their original scale (i.e., not Box-Cox transformed)

[c] These semen quality endpoints were measured only in the first sample and were modeled using logistic regression with fixed effects.

[d] These semen quality endpoints were measured in both the first and second samples and were modeled using logistic regression with Generalized Estimating Equations (GEE).

[e] Adjusted models accounted for age (continuous), abstinence time (continuous), alcohol consumption (categorical), body mass index (continuous), creatinine (continuous), education (categorical), income (categorical), previously fathered pregnancy (continuous), serum cotinine (continuous), study site (categorical), and race/ethnicity (categorical).