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Exposure to bisphenol-A and reproductive hormones among male adults

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ABSTRACT

Background: Bisphenol A (BPA) is a suspected human endocrine disruptor which is widely used.
Methods: In order to determine whether urine BPA level is associated with serum reproductive hormone levels among male adults, we carried out a cross-sectional study in China. We recruited 592 male workers and collected their urine samples for BPA measurement. We also collected blood samples and examined serum reproductive hormones. We used multiple linear regression and log-binomial model to examine associations between urine BPA level and hormone levels after controlling for age and smoking status.
Results: An increased urine BPA level was associated with increased prolactin ($p < 0.001$), estradiol ($p < 0.001$), sex hormone-binding globulin level ($p = 0.001$), and a reduced androstenedione ($p < 0.001$) and free androgen index level ($p = 0.021$). Males, whose urine BPA level was in the 2nd, 3rd and highest quartiles, had respectively 1.58, 1.33 and 3.09-fold increased prevalence of having a high prolactin level (>P_{75} level). The highest quartile of BPA level was associated with 1.63 and 1.50-fold increased prevalence of having a high estradiol and elevated sex hormone-binding globulin level. Males with higher quartile of BPA level had a lower inhibin B level.
Conclusion: High BPA exposure is associated with increased prolactin, estradiol and sex hormone-binding globulin level in males, and may contribute to male infertility.

Abbreviations: AD, androstenedione; AR, androgen receptor; BMI, body mass index; BPA, bisphenol A; CV, coefficient of variation; E2, estradiol; EDCs, endocrine disrupting chemicals; ELISA, enzyme-linked immunosorbent assay; FAI, free androgen index; FSH, follicle-stimulating hormone; FT, free testosterone; HPLC, high-performance liquid chromatography; INB, inhibin B; LOD, the limit of detection; PR, prevalence ratio; PRL, prolactin; RIA, radioimmunoassay; SHBG, sex hormone-binding globulin; T, total testosterone.

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1. Introduction

The prevalence of synthetic chemicals in our environment that are capable of mimicking estrogenic actions is a growing concern. One such chemical is bisphenol A (BPA). BPA is used to manufacture polycarbonate plastics and epoxy resins. Workers in epoxy resin and BPA manufacturing factories are occupationally exposed to BPA via inhalation and dermal contact. More than 90% of the workers had detectable BPA levels in their blood samples (He et al., 2009a). In addition, BPA can leach from a variety of resin-based and polycarbonate plastic products, including dental sealants and containers for foods and beverages, leading to widespread human exposure, with the presence of measurable concentrations of metabolites reported in the urine of more than 90% of population-representative samples (Calafat et al., 2008).

Our previous work have suggested associations between BPA and male sexual dysfunction (Li et al., 2010a,b), decreased sperm quality (Li et al., 2011), and disturbed male genital development in humans (Miao et al., 2011), although further research is needed to confirm these findings. Animal studies have shown that BPA can act as an endocrine disruptor, with both estrogenic and antiandrogenic effects (Lee et al., 2003; Chapin et al., 2008). Serving as an androgen receptor (AR) antagonist (Lee et al., 2003), BPA interrupts normal AR binding activity, which may account for reported associations with reproductive function (Li et al., 2010a,b; Vom Saal and Hughes, 2005), and potentially altering endocrine functions as well (Bonefeld-Jorgensen et al., 2007; Wetherill et al., 2007).

Numerous studies have demonstrated that BPA can alter endocrine function in animals. BPA-exposed neonatal Fisher 344 rat pups showed an increase in serum prolactin (PRL) level (Khurana et al., 2000). Exposure of pubertal rats to BPA decreased testosterone (T) levels (Akingbemi et al., 2004). However, results from animal studies may not apply to humans due to the species- and strain-differences in susceptibility to BPA (N'Tumba-Byn et al., 2012).

Compared with animal studies, human studies on BPA level and hormone levels are limited and inconclusive (Meeker et al., 2010; Hanaoka et al., 2002). Meeker et al. (2010) observed inverse relationships between urine BPA level and the free androgen index (ratio of testosterone to sex hormone binding globulin, FAI) and estradiol (E2) level in 167 men attending an infertility clinic. Mendiola et al. (2010) found a significant inverse association between urine BPA level and FAI level, as well as a significant positive association between BPA level and sex hormone-binding globulin (SHBG) level in 375 partners of pregnant women. While some studies found that higher daily BPA excretion was associated with higher total T level in men (Galloway et al., 2010; Lassen et al., 2014), the other study reported that BPA exposure was associated with lower T level (Cha et al., 2008). The conflicting finding may be due to different study population and BPA exposure levels. The demand and production capacity of BPA in China have grown rapidly (Huang et al., 2012). In addition to diet, workers are exposed to BPA via inhalation and dermal contact as well. We aim to examine the association between the urinary BPA level and hormone levels in a wide range of BPA exposure from an occupational population.

2. Materials and methods

2.1. Study population

From 2004 to 2008, we conducted a cross-sectional study to evaluate the health effects of BPA (Li et al., 2010a,b). We recruited exposed workers from one BPA manufacturer and three epoxy resin manufacturers in China. The exposed workers included those in the manufacturing process, packaging, technical supervisors, laboratory technicians, and maintenance workers. We also identified workers from factories where no known occupational exposure to BPA existed. The unexposed factories were from the same jurisdiction of the health department overseeing the participating BPA-exposed factories. To have better representation, the unexposed factories came from a variety of industries including construction material manufacturers, water supply factories, machinery factories, garment factories, a textile factory, manufacturers of electronics, machinery factories, fire stations and trade and commerce firms. The study was presented to all participating factories (both exposed and unexposed) as a study of health effects of general occupational hazards. No specific chemicals such as BPA were mentioned to blind participants to the study focus. Among 1101 eligible workers in four study sites, 684 agreed to participate in the study. The participation rate was 62.4% and 67.2% for exposed and unexposed workers respectively. A total of 592 (53.8%) workers who provided urine and serum samples were included in the final analysis; 165 of these workers were from exposed factories and 427 workers from unexposed factories.

2.2. In-person information

We obtained information on demographics and life style factors (smoking, alcohol and caffeine consumption) by in-person interview. Information on weight and height were not ascertained in the initial data collection. We obtained information on weight and height by telephone interview for workers who had contact information after the initial data collection and 181 males responded.

2.3. Urine BPA measurements

The field investigators were well trained to strictly follow the urine collection protocol, and HPLC operators had professional experience in chemical analysis. The containers for the biological sample were BPA-free. We collected one single spot urine sample from the unexposed males, as well as preshift and postshift urine samples from the exposed males. To make the measurement more stable, we averaged the BPA levels of the preshift and postshift samples. The urinary concentrations of total BPA were analyzed at the Department of Occupational Health and Toxicology, School of Public Health, a WHO Collaborating Center for Occupational Health, Fudan University, Shanghai, China. We measured urinary concentrations of total BPA (free plus conjugated species) through modified high-performance liquid chromatography (HPLC) as described

by He et al. (2009b). Briefly, urine samples were mixed with phosphorous acid buffer and β-glucuronidase (Sigma Chemical Co., St. Louis, MO) for hydrolyzation, and were then extracted twice with ether (HPLC grade; Dikma, Lake Forest, CA). The supernatants were collected and evaporated with nitrogen gas. The residue was dissolved in 60% acetonitrile (HPLC grade, Dikma) and analyzed by HPLC on the following parameters: column, Inertsil ODS-3, 4.6 mm × 250 mm, 5 μm; mobile phase A and B, acetonitrile/water (40:60, v/v), equivalent grade; flow: 1.0 mL/min; FLD, excitation wavelength 275 nm, emission wavelength 300 nm. Water was from Millipore Super-Q Plus water purification system (Bedford, MA). The BPA fraction was confirmed by use of standard BPA (HPLC grade, Shanghai Yuanxing Company) with the same HPLC base. We used the blank samples and a urine sample of standardized concentration at 4.5 mg/L in parallel analysis 5 times during every HPLC analysis to test the accuracy, and the concentrations were measured accurately. The limit of detection (LOD) was defined as the lowest concentration level than can be determined to be statistically different from a blank. The recommended value for the LOD is three times the standard deviation of replicate measurements of a blank or low-level sample (EPA, 2004). The LODs of BPA in the present study was 0.31 ng/mL, which is similar to the published LOD (Calafat et al., 2008; CDC, 2013). BPA levels below the LOD were assigned a value of LOD divided by the square root of 2, based on a conventionally accepted practice (Hornung and Reed, 1990). Adjustment for creatinine was performed to account for urine volume. Blank samples were randomly included during each HPLC analysis and no BPA was detected.

2.4. Serum hormones analysis

We drew venous blood samples from 9 am to 11 am, separated and froze the serum at −80 °C. We shipped all samples to the laboratory in Shanxi Medical University (Taiyuan, China) on dry ice and analyzed for hormone levels. We assessed serum follicle stimulating hormone (FSH), PRL, E2, and T through a commercially available radioimmunoassay (RIA) kits provided by China Diagnostics Medical Corporations (Beijing, China) (FSH: intraassay coefficients of variation [CV] < 5.4%, interassay CV < 9.5%, sensitivity < 0.27 mIU/mL; PRL: intraassay CV < 5.4%, interassay CV < 8.5%, sensitivity < 0.4 ng/mL; E2: intraassay CV < 6.0%, interassay CV < 7.7%, sensitivity < 5 pg/mL; T: intraassay CV < 7.4%, interassay CV < 9.5%, sensitivity < 0.02 ng/mL). We determined inhibin B (INB) using enzyme-linked immunosorbent assay (ELISA) kits provided by Adlitteram Diagnostic Laboratories (San Diego, USA) (sensitivity 1.0 pg/mL). We determined free testosterone (FT), SHBG, and androstenedione (AD) using ELISA kits provided by DRG International, Inc. (New Jersey, USA) (FT: intraassay CV 3.9%, interassay CV 6.2%, sensitivity 0.10 pg/mL; SHBG: intraassay CV 3.0–8.6%, interassay CV 7.2–11.6%, sensitivity 0.2 nmol/L; AD: intraassay CV 4.7–9.1%, interassay CV 8.8–12.1%, sensitivity 0.02 ng/mL). We used the control samples during each hormone analysis to ensure the accuracy of the results. All assays for hormones were performed in duplicate with the mean used for analysis.

2.5. Statistical analysis

We analyzed our data using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). The level of serum hormones and urine BPA levels were $\log_{10}$-transformed to correct their skewed distribution.

We compared the creatinine-adjusted geometric mean of urinary BPA for population characteristics by using Analysis of Variance (ANOVA). We used general linear regression to examine associations between urine BPA level and sex hormone levels after adjusting for potential confounders. We adjusted for the following factors which might be associated with BPA level and hormone levels: age and smoking status (current smoker vs. not current smoker). To make the results more interpretable, we also measured the associations using prevalence ratio (PR) based on dichotomized outcomes. We used log-binomial model (Deddens and Petersen, 2008) to examine the associations between quartiles of urine BPA level and higher hormone levels (>P_{75} level) after adjustment for potential confounders.

2.6. Ethics

The study was approved by the committees for protection of human subjects in Fudan University, Shanghai, China, Shanghai Institute of Planned Parenthood Research, Shanghai, China, and the Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, CA. The study complied with all applicable requirements of the USA and was in accordance with principles of the Declaration of Helsinki. All participants gave written informed consent before participation in the study.

3. Results

The mean age of the males was 31.7 ± 8.2 years (range: 16–63 years); 3.8% males were more than 50 years old. About 76.2% of the urinary samples had concentrations of BPA above LOD (0.31 ng/mL), with 98.2% in the exposed workers and 67.7% in the unexposed workers. Table 1 shows the characteristics of males and urine creatinine-adjusted BPA levels. Participants with more advanced education had relatively lower BPA levels. The most important determinant for a high BPA level in this study population was exposure to BPA in the workplace. There was no clear pattern of BPA distribution by age. Urine BPA level was not associated with marital status, smoking status or alcohol intake.

Table 2 presents the distributions of serum hormone parameters in the study population.

After adjustment for age and smoking status, we observed statistically significant associations between increasing urine BPA level and increased levels of PRL ($p < 0.001$), SHBG ($p = 0.001$), E2 ($p < 0.001$), and a reduced level of FSH ($p = 0.029$), AD ($p < 0.001$) and FAI ($p = 0.021$). There was no observed relationship between urine BPA level and total T, INB, or FT levels (Table 3). After further adjusting for BMI among a subset of participants who provided BMI information, the results were similar (data not shown).

To examine whether the observed associations demonstrated dose–response relationships between increasing urine

Table 1 – Characteristics of the study population and urine BPA levels.[a]

Characteristics	N	BPA level (μg/gCr)		p
		Median	Interquartile range (25th–75th percentiles)	
All	592	11.1	0.5–45.6	–
Age group (years)				
≤25	163	19.0	0–1653.5	<0.001
26–30	144	12.5	2.2–42.8	
31–35	134	7.5	0.4–23.2	
36–40	71	12.4	2.3–40.7	
>40	80	9.3	0–54.9	
Married				
No	281	10.8	0.6–46.0	0.328
Yes	311	11.1	0–45.1	
Education				
≤Junior high school	117	11.1	0.3–553.6	0.002
Senior high school	350	13.4	0.8–47.8	
≥College	125	5.4	0.3–23.6	
Current smoker				
No	202	6.5	0–121.2	0.479
Yes	390	12.6	1.1–39.4	
Alcohol intake				
No	460	11.1	0.4–46.9	0.846
Yes	132	11.1	1.0–43.5	
BPA exposure				
Exposed workers	165	685.9	43.7–3671.8	<0.001
Unexposed workers	427	4.2	0–15.9	

[a] Creatinine-adjusted BPA (μg/gCr).

BPA level and high serum hormone levels (>P_{75} level), we categorized the males into four groups according to the quartiles of urine BPA level. Males whose urine BPA level were in the 2nd, 3rd and highest quartiles had 1.58, 1.33 and 3.09-fold increased prevalence of having a high PRL level (>P_{75} level), respectively, compared with males with the lowest quartile of BPA level. Males with the highest quartile of BPA level had a 1.63 and 1.50-times greater prevalence of having an increased E2 level and SHBG level compared with males with the lowest quartile of BPA level. Males with higher quartile of BPA level had a lower prevalence of having an increased INB level (Table 4).

To determine the effect of BPA at environmental exposure levels, we examined associations between BPA level and hormone levels among unexposed workers who did not have occupational exposure to BPA in the workplace. Similar associations with various hormones remained, albeit they were no more statistically significant and a positive association was observed between BPA level and AD level in unexposed workers (Table 5).

4. Discussion

Our study is the first report to explore the relationships between urine BPA level and serum reproductive hormone levels in a large sample of Chinese male adults. A significant association was found between urine BPA level and serum

Table 2 – Distributions of serum hormones.

Hormone parameter	Mean	Standard deviation	Median	Interquartile range (25th–75th percentiles)	Range
FSH (mIU/mL)	2.9	2.6	2.2	1.2–3.8	0–29.2
PRL (ng/mL)	10.9	11.3	7.3	4.8–13.5	1.0–100.0
E2 (pg/mL)	48.6	48.2	38.5	27.5–55.9	1.4–550.0
T (ng/mL)	4.6	1.9	4.3	3.4–5.4	1.0–15.0
INB (pg/mL)	17.8	15.5	13.5	7.4–24.0	0.1–100.0
AD (ng/mL)	2.8	2.1	2.4	1.0–4.0	0.4–11.9
FT (pg/mL)	33.3	21.2	30.7	24.5–37.6	1.0–200.0
SHBG (nmol/L)	62.7	47.9	55.0	33.8–74.8	10.0–400.0
FAI[a]	11.3	9.6	8.4	5.3–14.0	0.4–66.3

[a] FAI: T × 100/SHBG.

Table 3 – Linear associations between urinary bisphenol A (BPA) level[a] and measurements of serum hormones.[b]

Hormone parameter	BPA (μg/gCr)	
	Adjusted β coefficient[c]	p
FSH (mIU/mL)	−0.0240	0.029
PRL (ng/mL)	0.0589	<0.001
E2 (pg/mL)	0.0362	<0.001
T (ng/mL)	0.0059	0.263
INB (pg/mL)	−0.0144	0.258
AD (ng/mL)	−0.0367	<0.001
FT (pg/mL)	0.0005	0.938
SHBG (nmol/L)	0.0293	0.001
FAI	−0.0234	0.021

β = regression coefficient.
[a] Creatinine-adjusted BPA (μg/gCr), log_{10}-transformed.
[b] Serum hormones levels were log_{10}-transformed.
[c] Adjusted for age, and smoking status (current smoker vs. not current smoker).

Table 5 – Linear associations between urinary bisphenol A (BPA) level[a] and measurements of serum hormones[b] among workers without occupational exposure to BPA (n = 427).

Hormone parameter	Adjusted β coefficient[c]	p value
FSH (mIU/mL)	0.0185	0.318
PRL (ng/mL)	0.0009	0.960
E2 (pg/mL)	0.0116	0.499
T (ng/mL)	0.0119	0.265
INB (pg/mL)	−0.0493	0.040
AD (ng/mL)	0.0488	0.009
FT (pg/mL)	0.0139	0.330
SHBG (nmol/L)	0.0138	0.436
FAI	−0.0019	0.924

[a] Creatinine-adjusted BPA (μg/gCr), log_{10}-transformed.
[b] Serum hormones levels were log_{10}-transformed.
[c] Adjusted for age, and smoking status (current smoker vs. not current smoker); β = regression coefficient.

PRL, E2 and SHBG level. BPA exposure was also associated with decreased AD and INB level.

BPA was detected in the urine samples in the unexposed workers, which indicated humans may be exposed to BPA via the other route in addition to occupational BPA exposure. In the general population, human exposure mostly occurs via residues contained in food or beverages. Additional routes, such as inhalation and dermal contact, could also contribute to the overall human exposure to BPA (Vandenberg et al., 2007; Zalko et al., 2011; Braun et al., 2011).

A positive association between urine BPA and E2 was found, which is consistent with one study (Lassen et al., 2014), but contradictory to the finding of another study, which reported an opposite relationship in men attending an infertility clinic (Meeker et al., 2010). The inconsistent finding may be due to differences in study population and exposure level. The BPA exposure level in our study as well as in Lassen and his colleagues' study was higher than that in Meeker and his colleagues' study (Meeker et al., 2010; Lassen et al., 2014). BPA can function as endocrine disrupting chemicals (EDCs) by acting as cell type-specific and concentration dependent agonists or antagonists for ERα and ERβ (Li et al., 2012). BPA has weaker estrogenic activity compared with E2 (Kim et al., 2001), but stronger activation was observed at higher concentrations. A competitive inhibition of the binding of E2 to ERs in the hypothalamus/pituitary would lead to an attenuation of the negative feedback of circulating E2 on LH, resulting in higher circulating LH concentrations, which would subsequently increase E2 production by the testis. Alternatively, BPA can also act on hypothalamus/pituitary mediated through an antagonistic effect of BPA on the AR (Lee et al., 2003), and thereby increase E2 production. Further study is needed to clarify the association between BPA and E2 in humans.

We found a positive association between BPA exposure and PRL level, which was in line with animal studies (Youn et al., 2002; Stoker et al., 1999; Tohei et al., 2001). The association may probably through the action on pituitary. As estrogen can stimulate PRL secretion by acting at the pituitary level (Watters et al., 2000), it is likely that an increased estrogen BPA concentration after BPA exposure contributes to an increased PRL level. It is also possible that BPA mimics estradiol and binds to estrogen receptors in both the anterior and posterior pituitaries. It can induce PRL gene expression, release, and cell proliferation in both primary anterior pituitary cells and GH3 cells (Steinmetz et al., 1997), thus stimulating PRL release. The results may be of important public health significance.

Table 4 – Dose–response relationship between urine bisphenol A (BPA) level[a] and serum hormone levels.

Hormone parameter	Adjusted prevalence ratio[b] (95% CI) for > P_{75} on hormone parameter			
	Lowest quartile	2nd quartile	3rd quartile	Highest quartile
FSH (mIU/mL)	Ref	1.22 (0.78–1.90)	0.77 (0.46–1.29)	1.28 (0.83–1.99)
PRL (ng/mL)	Ref	1.58 (0.97–2.56)	1.33 (0.80–2.22)	3.09 (2.03–4.71)
E2 (pg/mL)	Ref	0.79 (0.50–1.27)	1.10 (0.72–1.68)	1.63 (1.13–2.35)
T (ng/mL)	Ref	1.34 (0.89–2.01)	1.21 (0.80–1.84)	1.19 (0.79–1.81)
INB (pg/mL)	Ref	0.54 (0.35–0.81)	0.84 (0.59–1.19)	0.63 (0.44–0.92)
AD (ng/mL)	Ref	1.46 (1.01–2.12)	1.12 (0.75–1.69)	0.97 (0.63–1.49)
FT (pg/mL)	Ref	1.13 (0.75–1.70)	1.34 (0.92–1.95)	0.97 (0.65–1.45)
SHBG (nmol/L)	Ref	0.89 (0.57–1.41)	1.28 (0.85–1.94)	1.50 (1.02–2.20)
FAI	Ref	1.88 (0.95–2.82)	1.67 (0.91–2.56)	1.10 (0.69–1.77)

[a] Creatinine-adjusted BPA (μg/gCr).
[b] Adjusted for age, and smoking status (current smoker vs. not current smoker).

Studies in rats indicate that hyperprolactinemia, even when mild to moderate, is known to affect the quality of mature spermatozoa and their fertilizing potential (Aleem et al., 2005). Hyperprolactinemia, thereby, may be associated with male infertility due to either asthenozoospermia, oligozoospermia, or azoospermia (Merino et al., 1997).

We observed an elevated SHBG among males with higher BPA level, which was supported by a human study on environmental BPA exposure (Mendiola et al., 2010). We also observed an inverse association between BPA and FAI, which may be driven by the association between BPA and SHBG. As SHBG decreases with high level of androgens and increases with estrogen, BPA may exert its effects on SHBG by increasing the estrogenic action or decreasing the androgen action.

We also observed an inverse association between urine BPA level and AD level although the association between urine BPA level and AD level was not statistically significant when we categorized these two variables. AD can be synthesized in one of two ways. The primary pathway involves conversion of 17-hydroxypregnenolone to dehydroepiandrosterone by way of 17,20-lyase, with subsequent conversion of dehydroepiandrosterone to androstenedione via the enzyme 3-β-hydroxysteroid dehydrogenase. The secondary pathway involves conversion of 17-hydroxyprogesterone to androstenedione directly by way of 17,20-lyase. BPA exposure may decrease the production of AD level by reducing the expression of 3-β-hydroxysteroid dehydrogenase (Qui et al., 2013), or by inhibiting the activity of 17,20-lyase (Zhang et al., 2011). Adult men with AD deficit may manifest lessening of the libido and later impotence, which can be an explanation of our previous finding that higher BPA level is associated with lower sexual function (Li et al., 2010a,b). In more severe cases, a progressive attenuation of the secondary sexual characters has been observed (Bhasin and Jameson, 2005).

We also found that higher BPA level was associated with lower INB level. It is suggested that inhibin is synthesized in Sertoli cells and INB level reflects Sertoli cell function (Anawalt et al., 1996). Study in rats indicated that BPA may affect testicular functions in terms of Sertoli cell functions (Tohei et al., 2001) and therefore decrease the production of INB. It is reported that INB levels are significantly reduced in men with infertility problems compared to fertile men (Kumanov et al., 2006), which was in line with our previous work has found that BPA exposure was associated with reduction of sperm morphology and density (Li et al., 2011).

Our study had a number of strengths. First, urine BPA and serum hormones levels were quantitatively determined by two laboratories independently, therefore less likely to lead to information bias. Second, the relative large sample size in our study provided an opportunity to adjust for a number of potential confounders and the wide range of BPA exposure levels in our study population allowed us to examine the association that may not be feasible in populations with relatively uniform BPA exposure level.

Our study also has several limitations. First, the participation rate in our study is low. However, as no specific chemicals such as BPA were mentioned to blind participants to the study focus, potential participants were not aware of the specific hypothesis of the study. All potential participants were given equal opportunity to participate and no effort was made to select participants based on the exposure level. We also compared age, education, and employment history between participants and non-participants, and they were comparable. Therefore, it seems unlikely that the observed associations between serum BPA concentration and serum sex hormone levels could be explained by participation bias. Second, BPA is very rapidly metabolized, with an elimination rate of hours (Volkel et al., 2002). The single spot urine collected may reflect only very recent exposures and cannot characterize average BPA exposures for any individual. We based our BPA exposure assessment on both preshift and postshift urine samples in the exposed males. Still, the misclassification of BPA exposure cannot be avoided. Third, as a cross-sectional study, the associations we observed may reflect the recent BPA exposure and duration of hormone changes rather than the hormone changes themselves. Moreover, reverse causation is always a potential concern for this type of studies. However, high PRL would be expected to lead to lower BPA level (Gill-Sharma, 2009; Takeuchi et al., 2006), an opposite relation to what we observed. Thus, our results are unlikely as a result of reverse causation. Fourth, we cannot rule out confounding by unmeasured co-exposures that may co-occur with the study target. Our observation that similar associations also existed among unexposed workers (i.e., without occupational exposure to BPA), reduced the likelihood that the associations were due to other occupational chemical exposures.

5. Conclusion

In conclusion, our study indicates that BPA exposure may be associated with an increased serum PRL level and possibly other hormone levels in male adults. As hormones are involved in the regulation of male fertility, further studies will be needed to elucidate the association between BPA exposure and male infertility.

Authors' role

Xiaoqin Liu contributed to data preparation, analysis and interpretation of data, and drafted the manuscript. Maohua Miao contributed to study design, data analysis, interpretation of the results, and revised the manuscript. Zhijun Zhou contributed to acquisition of data and revised the manuscript. Ersheng Gao contributed to the study design, the interpretation of the results, and revised the manuscript. Jianping Chen contributed to acquisition of data and revised the manuscript. Jintao Wang contributed to acquisition of data and revised the manuscript. Fei Sun contributed to the design of the study and revised the manuscript. Wei Yuan contributed to the conception and the design of the study, the interpretation of the results, and revised the manuscript. De-Kun Li contributed to the conception and the design of the study, data analysis, the interpretation of the results, and revised the manuscript. He is also the Principal Investigator of the study and responsible for obtaining the NIOSH funding for the study. All authors approved the final manuscript.

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Conflict of interests

We declare we have no actual or potential competing financial interests.

Transparency document

The Transparency document associated with this article can be found in the online version.

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