

Occupational exposure to bisphenol-A (BPA) and the risk of Self-Reported Male Sexual Dysfunction

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BACKGROUND: Animal studies have suggested that bisphenol-A (BPA) is a potential human endocrine disrupter; but evidence from human studies is needed.

METHODS: We conducted an occupational cohort study to examine the effect of occupational exposure to BPA on the risk of male sexual dysfunction. Current workers from BPA-exposed and control factories were recruited. The exposed workers were exposed to very high BPA levels in their workplace. Male sexual function was ascertained through in-person interviews using a standard male sexual function inventory.

RESULTS: BPA-exposed workers had consistently higher risk of male sexual dysfunction across all domains of male sexual function than the unexposed workers. After controlling for matching variables and potential confounders, exposed workers had a significantly increased risk of reduced sexual desire [odds ratios (OR) = 3.9, 95% confidence interval: 1.8–8.6], erectile difficulty (OR = 4.5, 95% CI 2.1–9.8), ejaculation difficulty (OR = 7.1, 95% CI 2.9–17.6), and reduced satisfaction with sex life (OR = 3.9, 95% CI 2.3–6.6). A dose–response relationship was observed with an increasing level of cumulative BPA exposure associated with a higher risk of sexual dysfunction. Furthermore, compared with the unexposed workers, BPA-exposed workers reported significantly higher frequencies of reduced sexual function within 1 year of employment in the BPA-exposed factories.

CONCLUSIONS: Our findings provide the first evidence that exposure to BPA in the workplace could have an adverse effect on male sexual dysfunction.

Key words: bisphenol-A / epidemiology / occupational studies / cohort study

Introduction

Similar to diethylstilbestrol (DES), bisphenol-A (BPA) was first recognized in the 1930s to be a potential synthetic estrogen (Dodds and Lawson, 1938). However, unlike DES that was eventually selected for medicinal use and later discovered to be a carcinogen and to cause many other health problems (Giusti *et al.*, 1995; Swan, 2000; Klip *et al.*, 2002; Palmer *et al.*, 2006; Troisi *et al.*, 2007), BPA found its way into plastic production, mainly in the production of polycarbonated plastics and epoxy resins. BPA is contained in many consumer products

including baby bottles, plastic containers and the resin lining of cans used for food and beverages, as well as dental sealants (National Toxicology Program, 2008). Use of polycarbonate bottles has been shown to lead to increased urine BPA levels (Carwile *et al.*, 2009). Most human population could be constantly exposed to some levels of BPA. In a national sample of the US population, more than 90% of spot urine samples had detectable BPA with a median urine level of 2.7 µg/l (Calafat *et al.*, 2005; Calafat *et al.*, 2008; National Toxicology Program, 2008). Since BPA has a fast metabolism rate (half-life time <6 h) (National Toxicology Program, 2008), this finding suggests a continuous exposure to

BPA in the US population. Similar findings of BPA exposure have been reported in other countries as well (Kim *et al.*, 2003; Matsumoto *et al.*, 2003; Miyamoto and Kotake, 2006).

Animal studies have shown that BPA affects the male reproductive system including androgen receptors (ARs), male sex hormone levels, male reproductive organs including testes, epididymis, sperm and seminal vesicles, the prostate gland and sperm production (Richter *et al.*, 2007; National Toxicology Program, 2008). Changes in sexual behavior including a reduced performance in latency and frequency of intromission among rodents that had been exposed to BPA have also been reported (Farabollini *et al.*, 2002; Della *et al.*, 2006; Richter *et al.*, 2007). BPA has been shown to have both estrogenic and antiandrogenic effects in both *in vivo* and *in vitro* studies (Sohoni and Sumpter, 1998; Lee *et al.*, 2003; Xu *et al.*, 2005; Sun *et al.*, 2006; Wetherill *et al.*, 2007; National Toxicology Program, 2008). Nonetheless, some researchers have not observed any effects of BPA in their animal studies (Tyl *et al.*, 2002; Tyl *et al.*, 2008a, b). However, these findings of a lack of an observed BPA effect have been recently challenged by a group of scientists from more than 30 academic and research institutes (Myers *et al.*, 2009).

BPA has been considered a highly suspect human endocrine disruptor, likely affecting both male and female reproductive systems. However, the evidence of such effects of BPA from epidemiological studies of the human population remain lacking as noted by two US government panels convened by the National Toxicology Program and the National Institute of Environmental Health and Safety (Kuehn, 2007; vom Saal *et al.*, 2007; National Toxicology Program, 2008), respectively. Largely based on findings from animal studies, these two panels reached somewhat different conclusions on the potential effect of BPA as a human endocrine disruptor, leading to a widely publicized controversy. This controversy was further intensified after the recent tentative decision on BPA safety by the Food and Drug Administration (FDA) in the USA (<http://www.fda.gov/oc/opacom/hottopics/bpa.html>) was subsequently rebutted by its own Science Board (<http://www.time.com/time/health/article/0,8599,1855853,00.html>).

We have conducted an occupational cohort study to evaluate whether exposure to high levels of BPA affects male sexual functioning. Given its reported antiandrogenic and estrogenic effects and observed adverse effects on sexual behaviors and the male reproductive system in experimental animal models, the effect of BPA on male sexual dysfunction may be a sensitive endpoint not only relevant to male fertility, but also to other endpoints on which the effect is not as easily detected.

Materials and Methods

From 2004 to 2008, we conducted an occupational cohort study among workers of manufacturers of BPA and epoxy resin in China where relatively high exposure to BPA could be observed. Epoxy resin manufacturers use BPA as one of their raw materials. We collaborated with two Chinese academic and research institutions which were responsible for data collection for the study. The same data collection protocols were used for both the exposed and unexposed factories. The study was presented to all participating factories (both exposed and unexposed) as a study of health effects of general occupational hazards. Therefore, all participants were blinded to the specific hypothesis related to the effect of BPA. The

study was approved by the Institutional Review Boards of all three participating institutes, and all participants signed an informed consent form before participation in the study.

Exposed workers

In one participating BPA manufacturer and three epoxy resin manufacturers, all workers with exposure to BPA were eligible for the study. This included workers in the manufacturing process, packaging, technical supervisors, laboratory technicians, and maintenance workers. Among 373 eligible male workers, 230 (62%) agreed to participate in the study. Because current sexual function was ascertained, those who had left the factories ($n=46$) were excluded, since current BPA exposure for those retired workers was likely low, therefore not reflective of their previous exposure at work. In addition, it is unknown at this time whether the effect of BPA on sexual dysfunction is reversible after an extended period of absence of exposure. Inclusion of those retired workers would have likely led to misclassification of their exposure level based on their past exposure only.

Unexposed workers

In the same city where the BPA-exposed workers were recruited, we identified unexposed control factories where no known occupational exposure to BPA existed. The selection of control factories were based on the following factors. First, the factories were from the same jurisdiction of the health department overseeing the occupational health of the participating BPA-exposed factory. Second, the factories had no known BPA exposure in the workplace. Third, the factories had workers who met the selection criteria for age, education, gender and employment history. Fourth, the owners of the factories agreed to participate in the study. Fifth, the factories were not exposed to known reproductive toxicants. To have better representation, the control 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. Unexposed workers were matched to exposed workers on age (5 year interval), gender, educational level and length of employment. Among 515 identified eligible unexposed male controls, 284 (55%) agreed to participate in the study. To increase the sample size, we also included 120 male spouses whose wives were selected as unexposed controls for the BPA-exposed female workers. A total of 404 unexposed controls were available for analyses.

BPA measurement

For each of the four participating BPA-exposed factories, we conducted spot air sampling for each position in the manufacturing process, and personal air sample monitoring for each workplace with similar exposure levels. To determine workplaces with similar exposure, we collected exposure information according to the following steps. First, we thoroughly reviewed the factory's historical records including production capacity, remodelling history, and implementation of preventive measures. Second, we interviewed factory leaders and long-term workers about the history of BPA exposure to verify and supplement the information obtained from historical records. Third, our research team conducted a walk-through evaluation of each facility to determine the nature of BPA exposure and existence and utility of any preventive equipment. Fourth, we conducted in-person interviews with all participants to ascertain information on jobs held including start and end dates, changes of workplace and job titles, personal hygiene habits and use of protective equipment and exposures to other chemicals.

On the basis of the information obtained during these four steps, workplaces in each factory were categorized into subgroups with similar BPA

Table I TWA₈ levels of BPA in air samples of the BPA exposed factories (µg/m³)

Job title	Number of samples measured	Detectable rate	Median	Geometric mean	Percentile (25th–75th)
Packaging	18	0.94	8.18	15.67	2.53–299.65
Chemical reaction	67	0.96	2.16	4.1	0.85–11.00
Material feeding	17	0.88	15.31	4.35	0.47–26.40
Multitasking	63	0.87	4.88	8.33	3.35–17.67
Other*	15	0.93	4.49	3.52	1.74–5.73
Total average	180	0.92	4.57	5.97	1.46–16.30

*Includes laboratory test, storage, administration and mechanical maintenance.

exposure levels. Personal air sample monitoring was carried out for all subgroups of BPA exposure workplaces so that we would have BPA exposure levels from personal air sample monitoring for each subgroup. The personal air sample monitoring was carried out for the entire shift. We used the ESCORT ELF sampling pump with an inhalable fraction sampling head placed near the workers' inhalation level. Samples were collected at 2.0 l/min using glass fiber filters. The BPA content from personal sampling was analysed by high-performance liquid chromatography with its limit of detection at 0.20 µg/m³. The BPA exposure level during an 8-h shift was calculated using the Time-weighted Average (TWA₈) for each individual who carried out the personal sample monitoring. TWA₈ for a given BPA-exposed subgroup was the average of all individual TWA₈ in this workplace. Table I presents the results of BPA exposure levels at various workplaces in the BPA exposed factories. In addition, spot urine BPA levels in sub-samples of the BPA-exposed and -unexposed workers who provided urine specimens clearly showed that BPA exposed workers had much higher urine BPA levels than unexposed workers (Table II).

BPA exposure levels for participants were measured by a cumulative exposure index (CEI). CEI was calculated as follows: $CEI = \sum_{i=1}^n D_i \times TWA_{8i}$ where D_i was the work duration (years) in a given workplace (a BPA-exposed subgroup) and TWA_{8i} was the BPA exposure level in that workplace during the period. For current workers, we used TWA₈ (µg/m³) obtained through personal monitoring. For positions held in the past, we used TWA₈ obtained from the records of historical monitoring data. For those who had personal monitoring, we used their own personal TWA₈. For those who did not have personal TWA₈, we used the average TWA₈ for their job titles obtained from average personal monitoring of other workers with the same job titles in the same workplaces.

Outcome measurement

During an in-person interview in which we asked various questions regarding their demographic characteristics, work history, medical history, personal behaviors and sexual activities, we used The International Index of Erectile Function and the Brief Male Sexual Function Inventory (O'Leary *et al.*, 1995; Rosen *et al.*, 1997) to ascertain sexual functioning among participating male workers. Four domains of sexual function were ascertained: sexual desire, erectile function, orgasmic function and overall satisfaction with sex life. We excluded 20 exposed workers and 18 control workers who did not answer questions regarding sexual function largely due to a lack of sexual activities. In addition to current sexual function, we ascertained changes in sexual function (increase or decrease in sexual functions) since participants joined the BPA-exposed factories and corresponding unexposed factories to determine the timing of the impact of exposure to BPA on sexual function. The periods ascertained were 1 year or less after employment, 2–5 years and greater than 5 years. Because very few participants reported increases in sexual function after employment, we combined those who reported an increase with those who reported

Table II Distribution of urine BPA level (µg/gCr)* between the exposed and unexposed workers

Occupational exposure to BPA**	n	Percentiles	
		50th	25th–75th
No	254	1.2	0–11
Yes***	123	57.9	13–467

*Creatinine-corrected (µg/gCr).

**A subset of workers who provided urine samples.

***Pre-shift urine samples.

no change in sexual function. Therefore, the focus of the analysis was the frequency of decrease in sexual function. Those who did not have sexual activities during a given period (e.g. the first year of employment) were considered as missing from the analyses for this period.

Information on potential confounders were also ascertained during the in-person interview, including (i) demographic characteristics, (ii) factors that may influence sexual function including smoking, alcohol use, presence of chronic diseases and exposure to other chemicals and heavy metals, (iii) occupational history and (iv) sexual history.

Analyses

We employed the odds ratio (OR) and its 95% confidence interval (CI) to measure the association between exposure to BPA and the risk of male sexual dysfunction. We used logistic regression to estimate OR of male sexual dysfunction associated with BPA exposure after adjustment for potential confounders. The adjusted variables were chosen based on whether they were risk factors for male sexual dysfunction (e.g. age, smoking status, chronic diseases, etc.) or whether they impacted the estimated association between BPA exposure and the risk of male sexual dysfunction. SAS software was used to conduct the analyses.

Results

The BPA-exposed and -unexposed workers were comparable regarding many demographic characteristics (e.g. age, marital status, etc.), their history of chronic diseases that may affect sexual function, and smoking and alcohol-drinking habits (Table III). When compared with the unexposed workers, BPA-exposed workers were less likely to have a college degree and more likely to have a history of exposure to other chemicals. BPA-exposed workers had a slightly shorter employment history.

Table III Characteristics of BPA-exposed and -unexposed workers

Characteristics	Category	Unexposed (n = 386 ¹) (%)	Exposed (n = 164 ¹) (%)
Age	≤25	29 (7.5)	8 (4.9)
	25–30	66 (17.1)	41 (25.0)
	30–35	96 (24.9)	32 (19.5)
	35–40	83 (21.5)	31 (18.9)
	40–45	44 (11.4)	22 (13.4)
	>45	68 (17.6)	30 (18.3)
Education	≤Junior high	112 (29.1)	62 (37.8)
	Senior high	182 (47.3)	89 (54.3)
	≥College	91 (23.6)	13 (7.9)
Married	No	44 (11.4)	20 (12.2)
	Yes	342 (88.6)	144 (87.8)
Employment history (year)	<1	28 (7.3)	22 (13.4)
	1–5	81 (21.1)	50 (30.5)
	≥5	275 (71.6)	92 (56.1)
History of chronic disease ²	No	308 (79.8)	132 (80.5)
	Yes	78 (20.2)	32 (19.5)
Ever exposed to other chemicals or heavy metals ³	No	335 (86.8)	68 (41.5)
	Yes	51 (13.2)	96 (58.5)
Current smoker	No	118 (30.6)	59 (36.0)
	Yes	268 (69.4)	105 (64.0)
History of alcohol intake	No	279 (72.3)	112 (68.3)
	Yes	107 (27.7)	52 (31.7)

¹The number in each category may not match the total number due to missing values.

²Diseases that may impact male sexual function including urogenital diseases, autoimmune diseases, endocrine disorders, hypertension and other cardiovascular diseases, kidney diseases and injury to genital organs.

³Includes organic solvents, pesticides/herbicides and heavy metals (e.g. lead, mercury, etc.).

After adjustment for potential confounders including age, education, marital status, current smoking status, a history of chronic diseases and exposure to other chemicals, and employment history, the BPA-exposed workers had a significantly higher risk of sexual dysfunction among all indices measuring male sexual function in four domains (sexual desire, erectile function, orgasmic function and overall satisfaction with sex life), compared with the unexposed workers (Table IV). The exposed workers had a nearly 4-fold increased risk of reduced sexual desire (OR = 3.9, 95% CI 1.8–8.6), greater than 4-fold increased risk of erection difficulty associated with BPA exposure (OR = 4.5, 95% CI 2.1–9.8), more than 7-fold increased risk of ejaculation difficulty (OR = 7.1, 95% CI 2.9–17.6) and almost 4-fold increased risk of reduced overall satisfaction with sex life (OR = 3.9, 95% CI 2.3–6.6) (Table IV).

To examine the dose–response relationship, we used CEI to measure the amount of cumulative BPA exposure for each exposed worker. We divided the CEI level into tertiles. A dose–response relationship between a BPA cumulative exposure level and the risk of male sexual dysfunction was generally observed with increasing BPA exposure level being associated with greater risk of male sexual dysfunction except for the measure of sex desire (Table V), providing additional support for an underlying association between BPA exposure and the risk of male sexual dysfunction.

To assess the length of time that it took for BPA exposure to have an effect on the risk of male sexual dysfunction, we examined the changes in male sexual function in relation to the duration of

employment. When employment in a BPA-exposed factory lasted 1 year or less, BPA-exposed workers already experienced a significantly higher frequency of reduced sexual function compared with unexposed workers during the same period of employment. The BPA-exposed workers had more than 6-fold increased risk of having a reduction in frequency of intercourse (OR = 6.7) and ejaculation function (OR = 6.3), a 10-fold increased risk of having reduced satisfaction with sex life (OR = 10.0), more than 17-fold increased risk of having reduced sex drive (OR = 17.7), and a 15-fold increased risk of reduced ability to have an erection (OR = 15.0) (Table VI). Additional years of employment showed similar results.

To remove the potential interference of exposure to other chemicals, we conducted additional analyses after excluding those who had a history of exposure to other chemicals or heavy metals. The above observed associations between BPA exposure and the risk of male sexual dysfunction remained (Table VII).

Discussion

After the recent evaluation by the two US government-convened panels and the controversy between the FDA and its own Science Board, the question of the adverse effect of exposure to BPA on human health has raised substantial concern among the public because of widespread presence of BPA in the environment and in consumer products such as baby bottles and food and water containers (Kuehn, 2007; vom Saal et al., 2007; National Toxicology Program,

Table IV Exposure to BPA and the risk of male sexual dysfunction

Sexual function in the past 6 months	Category	Unexposed ¹	Exposed ¹	OR ² (95% CI)	aOR ³ (95% CI)
Erectile function					
Ability to have an erection	Usually ($\geq 50\%$ of time)	368 (95.6)	136 (84.5)	Reference	Reference
	Not usually ($< 50\%$)	17 (4.4)	25 (15.5)	4.0 (2.1–7.6)	3.9 (1.8–8.5)
Ability to have an erection hard enough for penetration	Usually ($\geq 50\%$ of time)	361 (94.0)	132 (82.0)	Reference	Reference
	Not usually ($< 50\%$)	23 (6.0)	29 (18.0)	3.4 (1.9–6.2)	3.8 (1.9–7.6)
Difficulty of having an erection	No difficulty	365 (96.1)	135 (84.4)	Reference	Reference
	Some difficulties	15 (3.9)	25 (15.6)	4.5 (2.3–8.8)	4.5 (2.1–9.8)
Orgasmic function					
Difficulty level of ejaculating	No difficulty	349 (97.5)	136 (86.1)	Reference	Reference
	Some difficulties	9 (2.5)	22 (13.9)	6.3 (2.8–14.0)	7.1 (2.9–17.6)
Level of ejaculation strength (0–10)	10	300 (84.3)	90 (57.0)	Reference	Reference
	0–9	56 (15.7)	68 (43.0)	4.0 (2.6–6.2)	3.5 (2.1–5.7)
Sexual desire					
Level of sex drive (0–10)	> 5	369 (95.8)	140 (87.0)	Reference	Reference
	0–5	16 (4.2)	21 (13.0)	3.5 (1.8–6.8)	3.9 (1.8–8.6)
Overall satisfaction with sex life					
Level of satisfaction (0–10)	10	305 (86.2)	95 (61.3)	Reference	Reference
	0–9	49 (13.8)	60 (38.7)	3.9 (2.5–6.1)	3.9 (2.3–6.6)

¹The number in each category of sexual function may vary due to missing values or absence of sexual activities (N/A).

²Crude odds ratio.

³aOR: adjusted odds ratio; 95% CI: confidence interval. Adjusted for age, education, marital status, current smoking status, presence of chronic diseases, exposure to other chemicals and occupational history.

2008). Therefore, studies of the effect of BPA on humans are critically needed to help establish prevention strategies and regulatory policies.

The results from the current study provide important evidence that exposure to BPA in the workplace significantly increases the risk of male sexual dysfunction. The finding was consistent for all four domains measuring male sexual dysfunction, all showing elevated risks associated with BPA exposure. The magnitude of the risk associated with BPA exposure was quite significant as well, ranging from more than 3-fold to more than 7-fold increased risk. The observed associations remained after controlling for many physiological and behavioral factors that may be related to sexual dysfunction between BPA-exposure and -unexposed workers. In addition, the dose–response relationship for observed associations further strengthens the findings. The combination of these findings supports a likely underlying link between exposure to high BPA levels and increased risk of male sexual dysfunction in the human population.

Furthermore, we also examined changes in workers' sexual function since they were first exposed to BPA in the workplace. Such a measure of change in sexual function in relation to the timing of exposure and the subsequent evidence of a significant reduction in sexual function after their employment in a BPA-exposed factory compared with the similar, but unexposed, workers provides additional support for a possible detrimental effect of BPA on the risk of male sexual dysfunction.

Both *in vitro* and *in vivo* experimental studies have provided consistent evidence to support our findings that BPA exposure increases the risk of male sexual dysfunction. The BPA effect in animal studies has been observed at low-dose levels similar to current human environmental exposure levels (Richter *et al.*, 2007). While sexual dysfunction in animal studies is difficult to conduct, several studies have reported

changes of sexual behavior including a reduced performance in latency and frequency of intromission among rodents that were exposed to BPA (Farabollini *et al.*, 2002; Della *et al.*, 2006; Richter *et al.*, 2007). In addition to the consistent evidence from the animal studies of the effect of BPA on the risk of sexual dysfunction, both *in vitro* and *in vivo* studies have provided evidence of underlying mechanisms for the observed association, including the effects of BPA on the ARs, on male sex hormone levels, on male reproductive organs including testes, epididymis, sperm and seminal vesicles, and prostate gland, and on sperm production (Richter *et al.*, 2007; National Toxicology Program, 2008). BPA has been reported to have both estrogenic and antiandrogenic effects (Sohoni and Sumpter, 1998; Lee *et al.*, 2003; Xu *et al.*, 2005; Sun *et al.*, 2006; Bonefeld-Jorgensen *et al.*, 2007; Richter *et al.*, 2007; Wetherill *et al.*, 2007; National Toxicology Program, 2008). BPA has been shown to act as an AR antagonist that interrupts normal AR binding activity and therefore the interaction between AR and endogenous androgens (Wetherill *et al.*, 2007). Such an interruption to the function of endogenous androgens by BPA could disturb normal male sexual functions including libido and erectile and orgasmic functions. In addition, BPA has been reported to interfere with the function of Leydig cells resulting in a reduction of testosterone biosynthesis (Akingbemi *et al.*, 2004) and to adversely affect several tissue and cell structures of male sex organs through various mechanisms including possible epigenetic effects (Richter *et al.*, 2007; Wetherill *et al.*, 2007). Therefore, our observed association between BPA exposure and the risk of male sexual dysfunction is biologically plausible and well supported by experimental studies.

We evaluated the potential existence of participation bias in our results by examining whether participants and non-participants had

Table V Dose–response relationship of the effect of exposure to BPA on the risk of male sexual dysfunction

Sexual function in the past 6 months	Category	Unexposed ¹	Exposed ¹ CEI tertile 1	aOR ² (95% CI)	Exposed ¹ CEI tertile 2	aOR ² (95% CI)	Exposed ¹ CEI tertile 3	aOR ² (95% CI)	Trend test P-value ³
Erectile function									
Ability to have an erection	Usually ($\geq 50\%$ of time)	368 (95.6)	48 (92.3)	Reference	48 (85.7)	Reference	40 (75.5)	Reference	
	Not usually (<50%)	17 (4.4)	4 (7.7)	2.3 (0.7–8.0)	8 (14.3)	3.5 (1.3–9.2)	13 (24.5)	5.7 (2.3–14.6)	<0.01
Ability to have an erection hard enough for penetration	Usually ($\geq 50\%$ of time)	361 (94.0)	48 (92.3)	Reference	46 (82.1)	Reference	38 (71.7)	Reference	
	Not usually (<50%)	23 (6.0)	4 (7.7)	1.8 (0.5–6.0)	10 (17.9)	3.9 (1.6–9.2)	15 (28.3)	5.4 (2.3–12.5)	<0.01
Difficulty of having an erection	No difficulty	365 (96.1)	46 (88.5)	Reference	50 (89.3)	Reference	39 (75.0)	Reference	
	Some difficulties	15 (3.9)	6 (11.5)	4.9 (1.6–15.5)	6 (10.7)	3.0 (1.0–8.7)	13 (25.0)	6.2 (2.4–15.8)	<0.01
Orgasmic function									
Difficulty level of ejaculating	No difficulty	349 (97.5)	47 (92.2)	Reference	47 (85.5)	Reference	42 (80.8)	Reference	
	Some difficulties	9 (2.5)	4 (7.8)	4.6 (1.2–17.8)	8 (14.6)	7.3 (2.5–21.4)	10 (19.2)	8.6 (2.9–25.5)	<0.01
Level of ejaculation strength (0–10)	10	300 (84.3)	29 (56.9)	Reference	37 (67.3)	Reference	24 (46.2)	Reference	
	0–9	56 (15.7)	22 (43.1)	4.1 (2.0–8.3)	18 (32.7)	2.3 (1.2–4.6)	28 (53.9)	4.7 (2.4–9.3)	<0.01
Sexual desire									
Level of sex drive (0–10)	>5	369 (95.8)	44 (88.0)	Reference	49 (87.5)	Reference	47 (85.5)	Reference	
	0–5	16 (4.2)	6 (12.0)	5.0 (1.6–15.7)	7 (12.5)	3.7 (1.3–10.4)	8 (14.6)	3.5 (1.2–9.8)	<0.01
Overall satisfaction with sex life									
Level of satisfaction (0–10)	10	305 (86.2)	35 (68.6)	Reference	36 (66.7)	Reference	24 (48.0)	Reference	
	0–9	49 (13.8)	16 (31.4)	3.3 (1.5–7.0)	18 (33.3)	3.2 (1.6–6.4)	26 (52.0)	5.5 (2.7–11.2)	<0.01

¹The number in each category of sexual function may vary due to missing values or absence of sexual activities (N/A).

²aOR: adjusted odds ratio; 95% CI: confidence interval. Adjusted for age, education, marital status, current smoking status, presence of chronic diseases, exposure to other chemicals and occupational history.

³Two-sided P-value from Cochran–Armitage trend test.

Table VI Exposure to BPA and changes in male sexual function

After employment in the factory for 1 year or less	Unexposed ¹ workers	Exposed ¹ workers	OR ² 95% CI	aOR ³ 95% CI
Decrease in frequency of intercourse				
No	173 (96.6)	63 (76.8)	Reference	Reference
Yes	6 (3.4)	19 (23.2)	8.7 (3.3–22.8)	6.7 (2.0–22.7)
Decrease in ejaculation function				
No	183 (98.4)	87 (87.9)	Reference	Reference
Yes	3 (1.6)	12 (12.1)	8.4 (2.3–30.6)	6.3 (1.3–30.8)
Decrease in ability to maintain an erection				
No	288 (99.0)	108 (88.5)	Reference	Reference
Yes	3 (1.0)	14 (11.5)	12.4 (3.5–44.2)	8.7 (1.8–41.2)
Decrease in satisfaction with sex life				
No	176 (98.3)	67 (82.7)	Reference	Reference
Yes	3 (1.7)	14 (17.3)	12.3 (3.4–44.0)	10.0 (2.2–46.4)
Decrease in sex drive				
No	275 (98.9)	104 (83.9)	Reference	Reference
Yes	3 (1.1)	20 (16.1)	17.6 (5.1–60.6)	17.7 (4.2–74.3)
Decrease in ability to have an erection				
No	289 (99.3)	110 (88.0)	Reference	Reference
Yes	2 (0.7)	15 (12.0)	19.7 (4.4–87.6)	15.0 (2.7–83.6)

¹The number in each category of sexual function may vary due to missing values or absence of sexual activities (N/A).

²Crude odds ratio.

³aOR: adjusted odds ratio; 95% CI: confidence interval. Adjusted for age, education, marital status, current smoking status, a history of chronic diseases, exposure to other chemicals and occupational history.

Table VII Exposure to BPA and the risk of male sexual dysfunction among those without previous exposure to other chemicals or heavy metals

Sexual function in the past 6 months	Category	Unexposed ¹	Exposed ¹	OR ² (95% CI)	aOR ³ (95% CI)
Erectile function					
Ability to have an erection	Usually ($\geq 50\%$ of time)	323 (96.7)	53 (79.1)	Reference	Reference
	Not usually ($< 50\%$)	11 (3.3)	14 (20.9)	7.8 (3.3–18.0)	10.6 (4.0–28.0)
Ability to have an erection hard enough for penetration	Usually ($\geq 50\%$ of time)	317 (95.2)	49 (73.1)	Reference	Reference
	Not usually ($< 50\%$)	16 (4.8)	18 (26.9)	7.3 (3.5–15.2)	8.4 (3.6–19.6)
Difficulty of having an erection	No difficulty	319 (96.4)	54 (80.6)	Reference	Reference
	Some difficulties	12 (3.6)	13 (19.4)	6.4 (2.8–14.8)	4.9 (2.0–11.8)
Orgasmic function					
Difficulty level of ejaculating	No difficulty	305 (97.8)	53 (81.5)	Reference	Reference
	Some difficulties	7 (2.2)	12 (18.5)	9.9 (3.7–26.2)	9.1 (3.2–25.7)
Level of ejaculation strength (0–10)	10	266 (85.8)	35 (53.8)	Reference	Reference
	0–9	44 (14.2)	30 (46.2)	5.2 (2.9–9.3)	4.9 (2.7–9.1)
Sexual desire					
Level of sex drive (0–10)	> 5	322 (96.4)	56 (82.4)	Reference	Reference
	0–5	12 (3.6)	12 (17.6)	5.7 (2.5–13.4)	6.0 (2.3–15.5)
Overall satisfaction with sex life					
Level of satisfaction (0–10)	10	269 (87.3)	34 (52.3)	Reference	Reference
	0–9	39 (12.7)	31 (47.7)	6.3 (3.5–11.4)	5.9 (3.1–11.1)

¹The number in each category of sexual function may vary due to missing values or absence of sexual activities (N/A).

²Crude odds ratio.

³aOR: adjusted odds ratio; 95% CI: confidence interval. Adjusted for age, education, marital status, current smoking status, presence of chronic diseases and occupational history.

different risk profiles and whether participation patterns differed between the exposed and unexposed cohorts. Given the limited information that was available for non-participants, we compared age and employment history between participants and non-participants and between the exposed and unexposed groups simultaneously. Non-participants were slightly older than participants and, consistent with age, had slightly longer employment history than participants. However, this pattern of slight difference between participants and non-participants was similar between exposed and unexposed groups. Finally, the dose–response relationships shown in Table V do not support the argument for participation bias as an explanation of our findings. While the instruments used in this study to ascertain sexual dysfunction have been used extensively in studies of human populations (O’Leary et al., 1995; Rosen et al., 1997), one may argue that self-reported sexual function may contain inaccuracies. Because neither the exposed nor unexposed workers were aware of the specific underlying hypothesis of the study, it was unlikely that any misreporting would have been different between the exposed and unexposed workers. Therefore, any such non-differential misreporting of sexual dysfunction by participants would likely have led to attenuation of the observed association. In other words, without such misreporting, the observed association would likely have been greater.

Another factor which could possibly impact self-reported sexual dysfunction, and hence the results of the study, is the levels of stress experienced by the exposed, compared with unexposed, workers. Although we did not collect information on stress from participants, there was no evidence that the exposed workers were in a more stressful work environment than the unexposed workers. In fact, a few of these exposed factories had more automated manufacturing processes which should make the working environment less stressful.

We included 120 male spouses whose wives participated in the study as unexposed controls for exposed female workers to increase the sample size for the unexposed cohort. The reasons for including them were as follows: first, they were not exposed to BPA in the workplace and second, they were measured in the same way as other participants in the study. Nevertheless, they were not matched to the exposed workers on age, educational levels and employment history, thus, the distribution on these variables were different from those in the exposed group, which led to the differing distributions of some characteristics in Table III. However, the information on these variables was collected, which allowed us to control for them in the multivariable analysis to achieve the same effect as the matching process. Therefore, our observed association between BPA exposure and the risk of male sexual dysfunction was independent of these potential confounders. Finally, excluding these 120 and using only the originally selected controls produced essentially the same results.

The CEI used in measuring BPA exposure level in this study is likely to reflect the cumulative BPA exposure level. As showed in Table II, the BPA exposure level in this occupationally exposed population was much higher than that of the non-occupationally exposed general population. Therefore, the findings from this study probably do not apply to populations that are exposed to low levels of BPA. In addition, the potential mechanisms of the observed association are not clear at this point, and, as with any

such observational studies, unmeasured confounders remain a possible explanation for the observed association. Finally, for some new workers (<10%), the exposure and outcomes were ascertained during relatively the same period. For them, the study could be considered as cross-sectional. However, for most participants, their BPA exposures were from periods before the outcome measurements.

In this occupational cohort study, we observed an increased risk of male sexual dysfunction associated with BPA exposure in the workplace. The observed association was consistent across all domains measuring male sexual function with a dose–response relationship. The large magnitude of the observed effect combined with its consistency across all measures of sexual dysfunction support a possible underlying association. While the results need to be replicated in other studies, our findings provide the first piece of evidence that exposure to BPA may have an adverse effect on male sexual functioning in the human population. This finding not only has public health implications for male fertility, but possibly for other health outcomes as well, since male sexual function may be a more sensitive and easily measured endpoint that provides early signals about the adverse BPA effects on other endpoints that are more difficult to study. On the other hand, it should be noted that the observed association may only apply to highly exposed workers and a similar effect in environmentally exposed lower dose remains unclear. Nevertheless, given the widespread exposure to BPA by the human population, this finding increases the need to examine the health effects of BPA in both occupationally and environmentally exposed populations.

Authors’ Role

D.-K.L. is the Principal Investigator of the study and was responsible for the overall study design, obtaining funding, supervising data collection, directing data analyses, interpreting results and preparing manuscript. Z.Z. was responsible for designing and supervising BPA measurement. D.Q. and M.M. were involved in data collection and data analyses, Y.H. and T.W. were involved in conduct of BPA measurement. J.W. and Q.Z. were involved in data collection. X.W. and J.F. were involved in data analyses. L.H. was involved in study design and obtaining funding. H.C. was also involved in the study design and obtaining funding. E.G., site-Principal Investigator in China, was involved in the study design and data analyses. W.Y. was responsible for data collection and involved in study design, data analyses and interpretation of the results.

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