American Journal of Men's Health
2018, Vol. 12(6) 2144–2151

DOI: 10.1177/1557988318799163
journals.sagepub.com/home/jmh
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Urinary Bisphenol A Levels and Male Fertility

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Abstract

Bisphenol A (BPA) is a high-production volume industrial chemical found in many consumer products. BPA is a suspected potent endocrine disruptor, with endocrine-disrupting properties demonstrated in animal studies. Few human studies have examined bisphenol A exposure in relation to male fertility and, results are divergent. The aim of the study is to examine the associations between urinary BPA concentration and male fertility. Bisphenol A urinary concentrations were measured using gas chromatography coupled with tandem mass spectrometry in 315 men under 45 years of age with normal sperm concentration (⩾15 mln/ml) recruited from a male reproductive health clinic. Participants were interviewed and provided a semen sample. BPA was detected in 98.10% of urine samples, with a median concentration of 1.87 µg/l (1.63 µg/ g creatinine). A multiple linear regression analysis identified a positive association between the urinary concentrations of bisphenol A 25th–50th percentile and total sperm sex chromosome disomy ($p = .004$). Also when modeled as continuous variable urinary BPA concentration increased total sperm sex chromosome disomy ($p = .01$). Urinary concentration of BPA also increase the percentage of immature sperm (HDS) ($p = .018$) and decrease motility ($p = .03$). The study provides evidence that exposure to BPA is associated with poorer semen quality. Future studies are needed to confirm these findings.

Keywords

environmental exposure to bisphenol A, semen quality, DNA fragmentation, sperm aneuploidy

Received May 18, 2018; revised August 6, 2018; accepted August 13, 2018

Bisphenol A (BPA) is a high-production industrial chemical used in the manufacture of polycarbonate plastics and epoxy resins and is present in a variety of consumer products such as water and baby bottles, thermal receipts, dental sealants, medical equipment or food and drink containers (Vandenberg et al., 2007). Dietary ingestion is considered the main route of human exposure to BPA due to leaching of BPA from packing materials into food items (Vandenberg et al., 2013). Other possible sources of route of exposure are inhalation of indoor dust and dermal contact (Vandenberg et al., 2013).

BPA exists in two different forms: conjugated and unconjugated forms in humans (Cantonwine, Hauser, & Meeker, 2013). The majority of BPA is metabolized in the liver by glucuronidation into the conjugated compound, which is a water-soluble, less biologically active and quickly excreted in urine (Cantonwine et al., 2013). The unconjugated form comprises up to 12% of the total BPA in the body and is considered to be the active form (Vandenberg et al., 2010). Unconjugated BPA concentrations in plasma and urine are very low among the general population, making detection of this fraction very

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difficult (Völkel et al., 2005). Analysis of total urinary BPA (sum of conjugated and unconjugated forms) has generally been used in biomonitoring studies as a biomarker of exposure to BPA (Völkel et al., 2008). Widespread and continuous to BPA in humans has been confirmed by studies from general population, in which >90% of participants had detectable levels of BPA in urine (Calafat, Ye, Wong, Reidy, & Needham, 2008; Kasper-Sonnenberg et al., 2012).

BPA has been reported to alter endocrine function in laboratory animals (Maffani, Rubin, Sonnenschein, & Soto, 2006; Susiarjo, Hassold, Freeman, & Hunt, 2007). Those endocrine-disrupting effects have been observed at both high and low dose concentrations that are relevant to human exposure. Animals studies have shown that exposure to BPA may affect male reproductive organs including the testes, sperm and seminal vesicles and sperm production (Richter et al., 2007). Although in humans, several recent studies assess the exposure to BPA and male fertility the presented results are inconsistent. Some studies have reported significant associations of urinary BPA concentrations with reduced sperm concentration, motility, and morphology (Li et al., 2011; Meeker et al., 2010; Lassen et al., 2014). Whereas Mandiola et al., 2010 reported no association between BPA and male semen quality (Mandiola et al., 2010). The results of the studies of urinary BPA concentrations and sperm DNA damage are inconclusive (Goldstone et al., 2015; Meeker et al., 2010). Meeker et al., 2010 identified increase in sperm DNA damage measured as the percentage of DNA in comet tail. Whereas the study investigated semen parameters in the general population of men reported a decrease in DNA fragmentation was observed (Goldstone et al., 2015).

This study adds to the previous human semen quality studies of non-occupational BPA exposure more statistical power by expanding outcome measures to include the assessment of main semen quality parameters (concentration, motility, computer-aided semen analysis [CASA] parameters, and sperm morphology), sperm DNA damage and sperm aneuploidy, and by assessment of semen quality and reproductive hormones among large number of subjects. Although several studies have explored the association between BPA exposure and male reproductive function, none have carefully assessed semen quality parameters (the main semen parameters, CASA parameters, sperm morphology, sperm DNA damage, and sperm aneuploidy) in one study.

According to current knowledge, no previous studies have assessed the relationship between environmental exposure to BPA and sperm aneuploidy. The present study was designed to evaluate the relationship between urine BPA level and semen quality (main semen parameters, CASA parameters), sperm DNA damage and sperm aneuploidy.

Materials and Methods

Study Participants and Data Collection

Males attending infertility clinic in Lodz, Poland for diagnostic purposes with normal semen concentration of ⩾15 mln/ml or (World Health Organization [WHO], 2010) between 2008 and 2011 were recruited. The details of the study population and recruitment were presented elsewhere (Jurewicz et al., 2014). Briefly, men under 45 years of age were eligible for study recruitment. All participants obtained and signed written informed consents prior to enrollment. Upon recruitment, a questionnaire was assigned to each participant to collect the data including demographic characteristics, occupational exposures, medical history and lifestyle factors. Additionally participants provided urine, saliva, blood and semen samples on the same day of their clinic visit. Cotinine level in the saliva was measured to verify the smoking status as previously described (Jurewicz et al., 2014).

Semen Analysis

After the abstinence period semen samples were generated via masturbation into polypropylene containers. Within an hour, the samples were liquefied and semen parameters of sperm concentration, motility and motion parameters were assessed according to WHO (WHO, 2010) guidelines. Sperm morphology was quantified using strict Kruger criteria to classify men as having normal or below normal morphology (Jurewicz et al., 2014). The details of information about semen parameters analysis have been previously described (Jurewicz et al., 2014).

Sperm DNA damage was assessed based on sperm chromatin structure assay (SCSA) using flow cytometry (DAKO Galaxym DAKO, Denmark) (ASRM 2006; Evenson et al., 1999). The full details of the analysis of sperm DNA damage are presented elsewhere (Jurewicz et al., 2015).

To assess sperm aneuploidy, multicolor FISH analysis was performed using DNA probes specific for chromosomes 13, 18, 21, X, Y (AneuVysion DNA Probe Kit, VYSIS) as previously described (Radwan et al., 2015). Based on this information about six types of chromosome disomies total disomy were calculated.

Urinary Bisphenol A Concentrations

Single, spot urine samples were collected and frozen at −20°C and sent to the laboratory in Department of Toxicology, Medical University of Gdańsk. Analyses were performed using gas chromatography (Varian GC-450) coupled with tandem mass spectrometry (Varian 220-MS, ion-trap mass spectrometer).

Three milliliters of urine were placed in 10-ml screw-cap glass tube followed by 50 µl of mixed internal standard solution and 750 µl of freshly prepared acetate buffer (1M, pH 5.0) containing 230 U of β-glucuronidase were added. Overnight incubation (at least 12 hr) at 37°C was performed. Then the sample was acidified with 450 µl of 80% formic acid and 3 ml of HEX:MTBE mixture (3:1, v:v) were added to the sample and tube was shaken for 10 min. After centrifugation the organic layer was transferred into open glass tube and the extraction was repeated. Combined extracts were cleaned-up with 200 mg of MgSO4 and 10 mg of PSA by shaking in hands for 1 min. Then 5 ml of cleaned extract were transferred into new open glass tube and evaporated to dryness under stream of nitrogen at 35°C. The residue was dissolved with 50 µl of BSTFA:TMCS (99:1) and derivatized for 30 min at 40°C. One microliter of final extract was analyzed by GC-MS/MS. The limit of detection was 0.5 µg/L.

Statistical Analysis

Data management and statistical analysis were performed with R statistical software (ver. 3) (R Core Team 2016). In case of the measurements below the limit of detection (LOD) 1/2LOD were imputed. The proportion of samples below the limit of detection (LOD) was 1.9%. Descriptive statistics for subjects grouped by demographic characteristics were calculated, along with the distributions of urinary bisphenol A, and semen quality, sperm DNA damage and sperm aneuploidy. Multiple least squares linear regression models were used to quantify the associations of urinary bisphenol A (explanatory variables) with selected sperm quality measures as dependent variables. All exposure data were log transformed to obtain a normal distribution. Additionally, motility, % of sperm with abnormal morphology, DFI, HDS were also subjected to shifted log transformation log(1+x), to obtain more systematic quasi-normal distributions.

Negative binomial regression models were utilized for sperm disomy with the count of disomy outcome as the dependent variable and bisphenol A, with potential confounders as the independent variables. Disomy counts in binomial regression models were log transformed.

Creatinine adjusted bisphenol A concentrations were categorized into 4 groups, first one consisted of values below limit of detection (LOD) to 25th percentile value, second-greater than the 25th percentile value to the median, third greater than the median to 75th percentile value, while the fourth group consisted of values greater than the 75th percentile. Additionally urinary concentrations of bisphenol A were presented as continuous variables and in categories below and above median.

Confounding factors in multiple regression models were predefined based on literature and biological consideration. The variables considered as the potential confounders included: sexual abstinence (continuous), age (continuous), smoking (yes/no), past diseases (yes/no), alcohol consumption (None or $<$ 1 drink/week, 1–3 drinks /week, 4–7 drinks per week). Additionally sperm disomy model were adjusted for sperm concentration and motility. A p-value less than .05 was considered significant.

Results

Demographic characteristics, semen quality parameters, sperm DNA damage, sperm aneuploidy, and urine bisphenol A concentration are presented in Tables 1 and 2. A total of 315 men who attended infertility clinics for diagnostic purposes were enrolled in the study, mostly with higher (41.6 %; $n = 131$) or secondary (37.8%; $n = 119$) education. The average age of the participants was 32.1 years. The average BMI was 26.8 $\pm$ 3.4 kg/m^2. Most of the participants were nonsmokers (71%; $n = 224$) (Table 1). Urinary concentrations of bisphenol A are presented in Table 2. The concentrations of total (free plus conjugated) bisphenol A were detected in 98.10% ($n = 309$) of samples. The geometric mean and 95th percentile concentrations 1.84 µg/l (1.64 µg/g creatinine) and 8.19 µg/l (6.13 µg/g creatinine) respectively. The mean semen concentration was 50.6 mln/ml ($SD = 52.4$, median 32.6) (Table 2). The mean percentage of DNA fragmentation index (DFI) was 16.5% ($SD = 11.4\%$) (median 14%), high DNA stainability (HDS) was 7.7% (SD 3.9%) (median 7.16%), total sex chromosome disomy was 1.11 ($SD = 0.22$) and total disomy was 1.72% ($SD = 0.92$) (median 0.82) (Table 2).

Bisphenol A concentration and the relevant male fertility outcomes are presented in Table 3. A p-value of .05 was defined as the level of statistical significance. A multiple linear regression analysis identified a positive association between the urinary concentrations of bisphenol A 25th–50th percentile and total sperm sex chromosome disomy ($p = .004$). Also when modeled as continuous variable urinary BPA concentration increased total sperm sex chromosome disomy ($p = .01$). Such statistically significant relation was not noticed in case of total sperm chromosome disomy. (Table 3). Urinary concentration of BPA also increase the percentage of immature sperm (HDS) ($p = .018$) and decrease motility ($p = .03$) (Table 3).

Discussion

To our knowledge, this is the first study to examine the relationships between urinary BPA concentrations and male fertility: main semen quality parameters, CASA parameters, sperm DNA damage and sperm aneuploidy.

Table 1. Characteristics of the Study Population ($N = 315$).

Characteristics	*N* (%)
Education, *n* (%)	
Primary and vocational	65 (20.63)
Secondary	119 (37.78)
Higher	131 (41.59)
Smoking determined by cotinine level, *n* (%)	
No	224 (71.11)
Yes	91 (28.89)
BMI (kg/m^2) *n* (%)	
< 25	106 (33.65)
$\geqslant 25$	209 (66.35)
mean (*SD*)	26.8 ± 3.4
median (min–max)	27.6 (18.3–39.5)
Duration of couple's infertility (years) *n* (%)	
1–2	120 (38.10)
2–3	104 (33.01)
3–5	45 (14.29)
>5	46 (14.60)
Past diseases, which may have impact on semen quality, *n* (%)	
No	276 (87.62)
Yes	39 (12.38)
Abstinence [days] *n* (%)	
<3	11 (3.49)
3–7	242 (76.82)
>7	16 (5.08)
Missing data	46 (14.60)
mean (*SD*)	5.0 ± 2.3
median (min–max)	5.0 (0.0–20.0)
Age [years]	
mean (*SD*)	32.14(4.23)
median (min–max)	31.60 (22.01–44.26)
Alcohol use, *n* (%)	
None or < 1 drink/week	104 (33.01)
1–3 drinks /week	163 (51.75)
Everyday	48 (15.24)

Note. Past diseases which may have impact on semen quality—mumps, cryptorchidism, testes surgery, testes trauma.

The results of the present study suggest that urinary levels of bisphenol A increase the percentage of immature sperm (HDS) and sperm sex chromosome disomy and decrease sperm motility. These findings suggest that environmental exposure to bisphenol A may affect semen quality. The results are in agreement with the study performed in Denmark where the quality of semen sampled from healthy young men attending a compulsory physical examination for military service were examined (Lassen et al., 2014). Lassen et al., 2014 reported a significant inverse association between BPA concentration in urine and sperm motility. Meeker et al., 2010 reported the increase in the interquartile range (IQR) of urinary BPA was associated with decline in sperm motility, concentration and morphology among partners of subfertile couples seeking treatment from a fertility clinic in Massachusetts USA (Meeker et al., 2010). Those findings were consistent with the results of the study performed in Slovenia among men who were also recruited through a fertility clinic. Total urinary BPA concentrations decrease sperm motility, sperm concentration and total sperm count (Knez, Kranvogl, Breznik, Vončina, & Vlaisavljević, 2014). Li et al., 2011 examined workers with environmental exposure to BPA and observed an inverse association between BPA and sperm concentration and total sperm count (Li et al., 2011). Additionally, in two recent studies in which BPA was measured in human plasma and seminal fluids, inverse associations were identified with sperm concentration and total sperm count (Vitku et al., 2015, 2016). On the other hand, no significant association between sperm motility and exposure to BPA was reported among fertile young men from 4 cities in United States (Mendiola et al., 2010).

In the present study, the urinary concentration of BPA was related to increase in the percentage of immature sperm. Only two studies asses the exposure to BPA and sperm DNA damage (Goldstone et al., 2015; Meeker et al., 2010). Meeker et al., 2010 identified increase in sperm DNA damage measured as the percentage of DNA in comet tail. Whereas in the study performed by Goldstone and co-workers 2015 a decrease in DNA fragmentation was observed (Goldstone et al., 2015).

In present study, an increase in sperm sex chromosome disomy was observed. Such relation was not noticed in case of total sperm chromosome disomy. According to current knowledge, no previous study examines the association between exposure to BPA and sperm aneuploidy. The sex chromosomes may be more sensitive to environmental exposure to BPA than other chromosomes. Sex chromosomes are thought to be more susceptible to aneuploidy, due to the presence of a single chiasma between these chromosomes at meiosis I (Hassold, Sherman, Pettay, Page, & Jacobs, 1991). That is why the effect of exposure to BPA was observed in only in sperm sex chromosome.

The diverse outcomes may be due to the differences in the selection of the study group (such as men attending an infertility clinic or men occupationally exposed to higher concentrations of BPA). Additionally the different biological fluids in which concentrations of BPA were measured or different confounding factors used in statistical models may affect the results.

Animal studies investigating the prenatal exposure to BPA have reported that male reproductive function may be impaired in multiple ways (Manfo, Jubendradass, Nantia, Moundipa, & Mathur, 2014). Bisphenol A has been identified to affect the structure of the testes, prostate

Table 2. Semen Quality, the Level of Reproductive Hormones and Urinary Concentrations of BPA Among Study Participants.

	Statistical variables								
Semen quality	25%	50%	75%	95%	Max	Mean ± *SD*	Geometric mean ± *SD*	*N*	Frequency of detection
Main semen parameters:									
Concentration (mln/ml)	22.5	32.6	85.77	125	360.0	50.6 ± 52.4	–	334	–
Motility (%)	46	55.0	66	83	99.0	55.7 ± 19.9	–	315	–
Sperm with abnormal morphology (%)	31.22	50.0	69.51	75.25	96.0	53.7 ± 23.9	–	315	–
CASA parameters									
VSL (μm/s)	37	43.1	50.7	61.41	77.1	43.6 ± 10.3	–	315	–
VCL (μm/s)	37.5	79	92.0	108	146	78.1 ± 16.8	–	324	–
LIN (%)	51	56	61	66.1	74	56 ± 6.4	–	315	–
Sperm aneuploidy									
Total sex chromosome disomy	0.98	1.12	1.26	1.75	2.00	1.11 ± 0.22	–	220	–
Total chromosome disomy	0	0.70	0.82	1.89	1.20	1.72 ± 0.92	–	220	–
DNA fragmentation index									
DFI	8.34	14.0	20.43	41.18	68.7	16.5 ± 11.4	–	262	–
HDS	5.22	7.16	9.31	13.46	30.70	7.7 ± 3.9	–	262	–
BPA concentration in urine									
BPA unadjusted (μg/l)	1.12	1.87	3.02	8.19	61.10	3.01 ± 5.39	1.84 ± 2.52	315	98.10%
BPA CR-adjusted (μg/g creat)	1.00	1.63	2.88	6.13	59.18	2.88 ± 4.78	1.64 ± 2.32	315	98.10%

Note. VSL = straight-line velocity; VCL = curvilinear velocity; LIN = linearity; DFI = DNA fragmentation Index; HDS = high DNA stainability; BPA = bisphenol A.

and epididymides, to influence the anogenital distance (AGD), to reduce the expression of hormones and to alter the gene expression profile. It may impair the development of hypothalamus and affect the expression of thyroid-specific genes (Manfo et al., 2014). Postnatal exposure to BPA may impair spermatogenesis, sperm function and sperm quality as a result of effects on the hypothalamic-pituitary-testicular axis (Manfo et al., 2014). Some evidence also suggests that BPA may directly affect spermatozoa through its action on fertility-related proteins present in these cells (Rahman et al., 2015, Wang et al., 2016).

Urinary concentrations of BPA in study subjects were similar to those reported in National Health and Examination Survey 2011–2014 (NHANES 2018) in adult men. The geometric means in present study were 1.87 ng/ml (1.63 ng/g creatinine) and 1.64 ng/ml in NHANES 2011–2014 (NHANES 2018).

The study was limited because of the selection of men from infertility clinics; therefore the results should be applied to that type of population. Due to the patient population used in the study there are probably confounding underlying causes of subfertility that are not assesses. To limit this disadvantage, only men with normal semen parameters according to WHO classification (WHO, 2010) were recruited (Jurewicz et al., 2014). A better population to would be unselected population of reproductive age men.

A single urine sample was used to assess BPA exposure and a single serum sample to describe hormone function. Mahalingaiah et al. (2008) maintained that, despite within-person variability in urinary BPA concentrations, a single sample is predictive of long-term exposure (over weeks to months) and provides good sensitivity to classify individuals in epidemiologic studies.

Additionally, only a single semen sample from each men, so the reliability of a single semen sample to represent semen quality over a longer period of time is not well characterized. However, two recent reports provide evidence that one sample may be representative of semen quality over several weeks in epidemiological studies (Francavilla et al., 2007; Zhu et al., 2016).

This is the first study, which assesses the semen quality, sperm DNA measures, and the sperm disomy (total disomy and sex chromosome disomy) in one study. Additionally, the total sperm disomy were not analyzed in relation to bisphenol A exposure. A detailed questionnaire performed among study participants allowed for control of confounding factors. The smoking status was confirmed by analyses the level of cotinine in saliva.

In conclusion, the study was designed to investigate the association between exposure to bisphenol A and male fertility measured by semen quality parameters, sperm DNA damage, sperm disomy. The results indicated that exposure to bisphenol A can increase the percentage

Table 3. Bisphenol A Concentration in Urine and Semen Quality and the Level of Reproductive Hormones-Categories of Urinary BPA Concentrations.

		BPA				BPA		
		Coef	95% CI	*p*		Coef	95% CI	*p*
Conc	<25th		0		<50th		0	
	25th–50th	0.05	[−0.08, 0.17]	.46				
	50th–75th	0.07	[−0.06, 0.19]	.29	⩾50 th	0.08	[−0.02, 0.17]	.14
	>75th	0.06	[−1.46, 1.58]	.94				
	Cont.	0.03	[−0.06, 0.11]	.52				
Motility	<25th	0			<50th	0		
	25th–50th	−1.49	[−9.01, 5.26]	.70				
	50th–75th	−0.68	[−8.36, 6.88]	.86	⩾50 th	3.00	[−1.74, 7.74]	.21
	>75th	−5.4	[−13.01, 2.2]	.16				
	Cont.	−2.44	[−0.26, 7.48]	**.03**				
Morph	<25th	0			<50th	0		
	25th–50th	0.13	[−7.18, 7.43]	.97				
	50th–75th	−1.16	[−8.43, 6.11]	.75	⩾50 th	−1.55	[−7.55, 4.44]	.61
	>75th	−0.29	[−3.03, 2.51]					
	Cont.	−1.42	[−6.38, 3.54]	.57				
VSL	<25th	0			<50th	0		
	25th–50th	−1.31	[−4.24, 1.61]	.38				
	50th–75th	−0.32	[−3.24, 2.59]	.83	⩾50 th	0.20	[−2.22, 2.61]	.87
	>75th	−0.23	[−3.54, 3.09]	.89				
	Cont.	−1.23	[−3.25, 0.79]	.23				
VCL	<25th	0			< 50th	0		
	25th–50th	−1.65	[−4.79, 1.50]	.30				
	50th–75th	−1.40	[−4.53, 1.73]	.38	⩾50 th	−0.83	[−3.41, 1.76]	.53
	>75th	−2.52	[−5.75, 0.71]	.13				
	Cont.	3.56	[−0.36, −4.61]	.08				
LIN	<25th	0			< 50th	0		
	25th–50th	−0.68	[−2.55, 1.18]	.47				
	50th–75th	0.44	[−1.42, 2.30]	.64	⩾50 th	0.002	[−1.54, 1.54]	.99
	>75th	0.20	[−1.53, 2.20]	.55				
	Cont.	−0.41	[−1.68, 0.86]	.53				
% of sex chromosome disomy	<25th	0			< 50th	0		
	25th–50th	0.25	[0.09, 0.41]	**.004**				
	50th–75th	0.09	[−0.04, 0.22]	.16	⩾50 th	0.18	[−0.03, 0.38]	.10
	>75th	0.07	[−0.03, 0.25]	**.15**				
	Cont.	0.21	[0.05, 0.37]	**.01**				
% of total chromosome disomy	<25th	0			< 50th	0		
	25th–50th	−0.05	[−0.22, 0.13]	.60				
	50th–75th	−0.02	[−0.15, 0.10]	.74	⩾50 th	−0.05	[−0.22, 0.13]	.60
	>75th	−0.05	[−0.24, 0.15]	.62				
	Cont.	−0.06	[−0.23, 0.11]	.50				
DFI	<25th	0			< 50th	0		
	25th–50th	0.29	[−0.22, 0.80]	.26				
	50th–75th	−0.02	[−0.25, 0.22]	.89	⩾50 th	0.06	[−0.15,0.28]	.57
	>75th	−0.13	[−0.4, 0.15]	.36				
	Cont.	0.01	[−0.09, 0.28]	.29				
HDS	<25th	0			< 50th	0		
	25th–50th	−0.03	[−0.19, 0.13]	.73				
	50th–75th	0.09	[−0.07, 0.25]	.25	⩾50 th	0.003	[−0.13, 0.13]	.97
	>75th	0.08	[−0.35, 0.22]	.64				
	Cont.	0.13	[0.02, 0.24]	**.018**				

Note. Statistically significant at the level .05; coef-ß coefficient;
Multivariate model adjusted for: sexual abstinence, age, smoking, alcohol consumption, past diseases. VSL = straight-line velocity; VCL = curvilinear velocity; LIN = linearity; DFI = DNA fragmentation Index; HDS = high DNA stainability; BPA = bisphenol A.

of immature sperm (HDS) and sperm sex chromosome disomy and decrease sperm motility.

The results of the current study support the hypothesis that endocrine-disrupting chemicals are important factors for declining male semen quality. Those findings need to be confirmed in future studies.

Authors' Note

The work was done at the Nofer Institute of Occupational Medicine, Lodz, Poland.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was performed under the project "The association between environmental exposure to widespread man made endocrine disrupting chemicals and level of hormones associated with the activity of hypothalamic pituitary testicular axis among young men" supported by National Science Centre in Poland from grant no. UMO-2014/13/B/NZ7/02223 and the project financed with a grant for statutory activity IMP 10.30/2018.

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