In Utero Exposure to Bisphenol-A and Anogenital Distance of Male Offspring

Maohua Miao,[1,2] Wei Yuan,[2*] Yonghua He,[3] Zhijun Zhou,[3] Jintao Wang,[4] Ersheng Gao,[2] Guohong Li,[5] and De-Kun Li[1*]

[1]Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, California
[2]Department of Epidemiology and Social Science on Reproductive Health, Shanghai Institute of Planned Parenthood Research, World Health Organization Collaborating Center for Research in Human Reproduction, National Population and Family Planning Key Laboratory of Contraceptive Drugs and Devices, Shanghai, China
[3]Department of Occupational Health and Toxicology, School of Public Health and World Health Organization Collaborating Center for Occupational Health, Fudan University, Shanghai, China
[4]Department of Epidemiology, Shanxi Medical University, Taiyuan, China
[5]Institute for the Prevention and Treatment of Occupational Diseases, Baling Petrochemical Company, Yueyang, China

Received 1 April 2011; Revised 2 June 2011; Accepted 7 June 2011

BACKGROUND: Bisphenol-A (BPA) is an endocrine disruptor with widespread human exposure. The effect of in utero BPA exposure on human offspring remains largely unknown. **METHODS:** Anogenital distance (AGD) of sons of workers who did or did not have occupational BPA exposure during pregnancy were compared in an occupational cohort study. Parental BPA exposure level during the index pregnancy was estimated through a job-exposure matrix based on personal air sampling measurement. Maternal exposure was considered direct in utero exposure to the fetus, whereas paternal exposure was considered indirect in utero exposure. **RESULTS:** A total of 153 boys were included in the final analysis, among them 56 with parental occupational exposure during pregnancy and 97 without. After controlling for the boys' ages and weights using linear regression, parental occupational exposure to BPA during pregnancy was associated with shortened AGD in male offspring. The association was stronger for maternal exposure ($p < 0.01$). There was also a dose-response relationship with increased BPA exposure levels in pregnancy associated with greater magnitude of shortened AGD in male offspring, with a statistically significant trend for the association ($p = 0.008$). **CONCLUSION:** Our findings provide the first epidemiologic evidence that in utero BPA exposure may adversely affect male genital development. *Birth Defects Research (Part A) 91:867–872, 2011.* © 2011 Wiley-Liss, Inc.

Key words: bisphenol-A; anogenital distance, in utero exposure; occupational exposure; endocrine disruptor

INTRODUCTION

Bisphenol-A (BPA) is a monomer used primarily in the manufacturing of polycarbonate plastics and epoxy resins. BPA can be found in food and drink containers, plastic baby bottles, food and beverage can linings, and dental fillings. Because the ester bonds in these BPA-based polymers are subject to hydrolysis, leaching of BPA has led to widespread human exposure (vom Saal and Hughes 2005; Le et al., 2008). It has been reported that urine BPA levels increased after people used BPA-containing polycarbonate bottles (Carwile et al., 2009). In a recent U.S. study, urine BPA was detected in 92.6% of a national sample (Calafat et al., 2008).

Animal studies show that BPA can act as an endocrine disruptor, with both estrogenic and antiandrogenic effects. Serving as an androgen receptor (AR) antagonist, BPA interrupts normal AR binding activity and therefore may affect the morphology and function of male reproductive organs (Wetherill et al., 2007, vom Saal and

Presented at the 43rd annual meeting of the Society for Epidemiological Research, June 23–25, 2010, Seattle, Washington.
Supported by a grant from the U.S. National Institute of Occupational Safety and Health (R01 OH007580) and by the National basic research program of China (973 program) 2010CB529505
*Correspondence to: De-Kun Li, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612. E-mail: dkl@dor.kaiser.org and;
(For readers in China) Wei Yuan, Department of Epidemiology and Social Science on Reproductive Health, Shanghai Institute of Planned Parenthood Research, Shanghai, China, 200032. E-mail: yuanwei11@yahoo.com
Published online 26 August 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/bdra.22845

Hughes 2005). In particular, in utero exposure to BPA was found to produce harmful effects on reproductive organs in rodents, including changes in prostate gland weight, alteration in the development and tissue organization of the mammary gland, disruption of sexual differentiation in the brain and long-term deleterious effects in the vagina (Schonfelder et al., 2002). More importantly, these effects can be detected even at low doses of typical environmental exposure.

In utero exposure to AR antagonist agents has been shown to demasculinize and feminize male offspring in rodents (Wolf et al., 2004) and cause a cluster of male reproductive tract disorders, including shortened anogenital distance (AGD), hypospadias, and cryptorchidism, as well as adult-onset disorders such as low sperm count and testicular cancer (Hsieh et al., 2008; Welsh et al., 2008). Among them, AGD was considered as a sensitive marker of androgenic and antiandrogenic effects of in utero chemical exposure, and it has been recommended as one of the endpoints for examining the reproductive toxicity of chemicals by the U.S. Environmental Protection Agency (Foster and McIntyre, 2002). Strong correlations between AGD and all semen parameters have been reported in adult humans (Eisenberg et al., 2011; Mendiola et al., 2011). In the case of BPA, decreased AGD in rodent offspring has been found after maternal exposure to BPA during pregnancy (Ema et al., 2001; Kim et al., 2001; Murray et al., 2007). However, inconsistent results showing no change or increased AGD also exist (Gupta, 2000; Kobayashi et al., 2002; Howdeshell, 2008). The discrepancy in animal species, administration route, and exposure dosage make the comparison of existing studies difficult. No human studies have reported on the relationship between in utero BPA exposure and AGD in offspring, whereas decreased AGD has been found to be correlated with prenatal exposure to other environmental endocrine disruptors, such as phthalates and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) in humans (Swan et al., 2005; Torres-Sanchez et al., 2008). In the present study, we examined whether in utero BPA exposure, as measured by parental occupational exposure to BPA during pregnancy, has any effect on AGD of male offspring.

MATERIALS AND METHODS

Study Population

The population for this study was identified from participants of a study evaluating the health effects of BPA. A detailed description of the original study can be found elsewhere (Li et al., 2010b). In brief, a retrospective cohort of BPA-exposed workers and their families was recruited from manufacturers of epoxy resin in China, and corresponding unexposed workers were recruited from a variety of industries without BPA exposure in the same areas from 2004 to 2008, including construction material manufacturers, water supply factories, machinery factories, a textile factory, fire stations, and trade and commerce firms. More detailed descriptions of industry types are provided in a previous publication (Li et al., 2010b). Sons of workers were recruited if they agreed to a physical examination, including the measurement of AGD. The study was approved by the committees for protection of human subjects from all participating institutes. All participating families gave written informed consent before participation in the study. Parents provided consent for their younger participating children. Children who were 18 years or older provided their own consent.

In the original parent study, the participation rates were 61.66% for male workers (62.44% and 61.02% for exposed and unexposed groups, respectively) and 64.42% for female workers (77.85% and 60.27% for exposed and unexposed groups, respectively). Sons of BPA-exposed parents were eligible for the current study if either of their parents were involved in BPA-exposed occupations when they were in utero (i.e., when their mother was pregnant with them). All sons of unexposed workers (controls) were eligible. Of the 194 eligible boys, 153 boys participated in the study, the participation rate was 78.86% (72.72% and 82.90% in exposed and unexposed group, respectively). Among them, 97 boys were from unexposed parents and 56 boys had parents who were exposed to BPA during the index pregnancy. Of those, 15 had a mother who was exposed to BPA in the workplace during the index pregnancy, 38 had a father who was exposed to BPA in the workplace while his wife was pregnant with the index child, and 3 had a mother and father who were both exposed to BPA in the workplace.

Measurement of BPA Exposure

Parents were first classified into *exposed* or *unexposed* categories based on whether they were employed at the BPA-exposed factories during the index pregnancy. To further measure BPA exposure level for exposed workers, personal air sample monitoring was performed to obtain their current exposure level. The 8-hour time-weighted average (TWA_8) was then calculated to measure the BPA exposure level of a given job title based on the personal air sample monitoring results from this job title. A detailed description of TWA_8 measurement can be found in a previous publication (Li et al., 2010b). Past exposure level was estimated based on the combination of the current exposure level, employment history, change in manufacturing process and work environment, and use of protective measures. A job-exposure matrix was then constructed to provide BPA exposure level (estimated TWA_8) during the index pregnancy.

We also assayed urine BPA levels among the participants who provided their urine samples. The results based on these urine BPA samples have been previously reported (He et al., 2009a, 2009b). Although the current urine BPA level was not used as a measure of exposure level for the index pregnancy, it was used as an additional measure to verify the validity of classification of BPA exposure (see later).

Physical Examination and Measurement of AGD

All participating boys had a physical examination in which their body weight and height were measured, and their external genitalia were examined for any anomalies. Following the standard method described in the literature, AGD was measured from the center of the anus to the anterior base of the penis by the same physician using a measuring instrument with increments of 1 mm, while the boys were in a dorsal decubitus position with both hips flexed, as shown by Romano-Riquer (2007). The examining physician was blinded to the exposure status of the participants.

In-Person Interview

An in-person interview was performed by trained interviewers with all the participating workers and their spouses to collect the following information: sociodemographic characteristics, reproductive and medical history, health-related behaviors, exposure to environmental hazards, and employment history. In addition for the mothers, information about the index pregnancy was collected on gestational age, illnesses, medications, and other environmental risk factors during the index pregnancy, as well as information on birth outcomes such as birth weight and any gross abnormalities of newborns.

Data Analysis

Because AGD is a continuous variable, AGD for boys was compared between exposed and unexposed groups using multiple linear regression models after controlling for age and weight. To avoid the large variation caused by pubertal development, we did subgroup analysis among the boys aged less than 8 years, as the onset of puberty in the majority of boys (more than 95%) starts after that age (Monteilh et al, 2011; Tomova, 2010). All observations in the present study were independent because only one child from each family participated in the study.

BPA exposure during the index pregnancy was further divided into several dose categories. Because paternal exposure is considered an indirect maternal exposure during pregnancy (e.g., through contamination or maternal visits to factories), which is the relevant exposure level, paternal exposure was classified into lower exposure categories than direct maternal exposure. Parents who were both exposed to BPA in the workplace during the index pregnancy were considered as the highest exposure category. To test the validity of this classification, we compared the urine BPA level of those exposure categories among a subgroup of participants who also provided urine specimens for BPA assay.

Categorical variables were used to examine the effect of different BPA exposure levels for parental unexposed, paternal low TWA_8, paternal high TWA_8, maternal low TWA_8, maternal high TWA_8, and parents both exposed. We also used continuous variables, with the values of 1 through 6 corresponding to these categories, to examine the trend of a dose-response relationship. The weight of the boys was included in the model instead of height because weight was reported to be related to AGD in previous studies (Swan et al., 2005).

RESULTS

The age range of the participating boys was 0 to 17 years old, with 81% of them younger than 10 years. As shown in Table 1, boys with maternal BPA exposure were younger and had slightly lower birth weight compared to those with paternal BPA exposure or without parental exposure. Boys with paternal BPA exposure were more likely to be the result of a first pregnancy. Average maternal ages were similar in the three groups. No mother smoked during the index pregnancy, whereas 40 to 60% of the boys' fathers smoked, with the highest percentage among the paternal exposure group. The lengths of working during the index pregnancy were shortest for the mothers exposed to BPA in the workplace.

After controlling for the boys' age and weight, parental exposure to BPA in the work place during the index pregnancy was correlated with a shortened AGD in male offspring: compared with boys from unexposed families, AGD was 8.11 mm shorter on average for boys with maternal exposure ($p = 0.003$) and 2.87 mm shorter for those with paternal exposure ($p = 0.15$; Table 2). Similar results were found when the analyses were restricted to boys younger than 8 years to reduce the effects of pubertal

Table 1
Characteristics of Male Offspring in BPA-Exposed and Unexposed Groups

Variables	BPA-exposed during pregnancy: Mother exposed[a] (n = 18)	BPA-exposed during pregnancy: Father exposed[b] (n=38)	Unexposed (n = 97)
Average age (years)[c]	4.28 (2.19)	5.34 (4.71)	6.05 (4.23)
Average birth weight (gm)[c]	3415.00 (455.54)	3455.40 (582.11)	3597.87 (518.26)
Average maternal age at birth (years)[c]	26.50 (1.92)	25.71 (2.36)	26.47 (2.23)
Average paternal age at birth (years)[c]	28.38 (1.41)	28.07 (2.26)	28.35 (2.61)
Maternal education at birth			
Middle school or less	1 (5.56%)	15 (39.47%)	25 (25.77%)
High school	13 (72.22%)	18 (47.37%)	50 (51.55%)
College or more	4 (22.22%)	5 (13.16%)	22 (22.68%)
Paternal education at birth			
Middle school or less	2 (11.11%)	8 (21.05%)	12 (12.37%)
High school	10 (55.56%)	27 (71.05%)	45 (46.39%)
College or more	6 (33.33%)	3 (7.89%)	40 (41.24%)
Gravidity			
1	8 (44.44%)	21 (55.26%)	37 (39.36%)
2	6 (33.33%)	9 (23.68%)	42 (44.68%)
>2	4 (22.22%)	8 (21.06%)	15 (15.96%)
No. of paternal smoking during pregnancy	7 (38.89%)	22 (57.89%)	48 (49.48%)
Average working weeks of mother during the index pregnancy[c]	25.00 (14.24)	30.95 (13.76)	27.44 (13.53)

[a]Three boys with both mother and father exposed were included in the maternally exposed group.
[b]Paternal exposure with indirect maternal exposure.
[c]Mean ± SD. BPA, bisphenol-A.

Table 2
Parental BPA Exposure in Relation to Anogenital Distance of Male Offspring

Group	N	Mean ± SD (mm)	Coefficient[a]	*p* value
All subjects				
Unexposed	97	87.44 (19.39)	Reference	
Father exposed only	38	81.84 (19.84)	−2.87	0.15
Mother exposed[b]	18	71.94 (8.60)	−8.11	0.003
Among boys <8 years old				
Unexposed	68	78.71 (11.22)	Reference	
Father exposed only	27	71.48 (10.27)	−3.78	0.07
Mother exposed[Δ]	17	70.88 (7.55)	−7.65	0.002

[a]Adjusted for age and weight of male offspring.
[b]Three boys with both mother and father exposed were included in the mother-exposed group. BPA, bisphenol-A.

development. In fact, the association was slightly stronger among these younger boys. Additional adjustment for body mass index, maternal age and education, and paternal age and education produced similar results, as well as adjustment for gravidity and paternal smoking.

The association between BPA exposure during pregnancy and AGD also showed a dose-response relationship, with the inverse correlation becoming stronger with increasing BPA exposure dose: the coefficients were −2.74, −3.27, −5.77, −10.89, and −11.91 for boys with paternal low TWA_8, paternal high TWA_8, maternal low TWA_8, maternal high TWA_8, and both parents exposed, respectively, compared with boys from unexposed families in linear regression analysis. The trend test was highly statistically significant ($p = 0.0008$; Fig. 1).

The validity of the dose categories based on types of parental exposure was confirmed by the tests of BPA levels among a subgroup of participants that provided urine specimens. The urine BPA levels showed a gradient reduction from exposed female workers (maternal direct exposure) to spouses of exposed male workers (maternal indirect exposure through paternal exposure) to unexposed women. The geometric mean (95% confidence interval [CI]) of maternal current urine BPA was 16.0 (9.1–28.0; n = 18), 2.2 (1.5–3.3; n = 38), and 0.6 μg/g Cr (0.7–0.9; n = 93) in exposed mothers, spouses of exposed fathers, and unexposed mothers, respectively. Among each of the paternal and maternal exposed categories, we

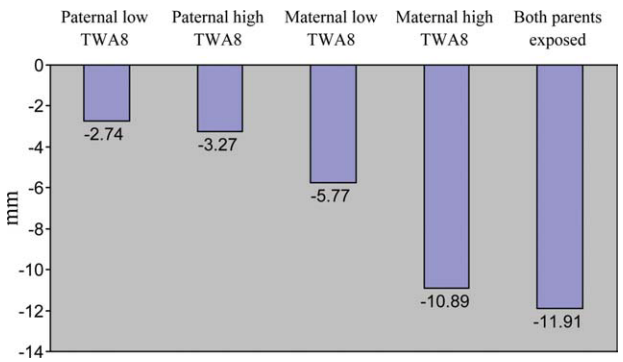

Figure 1. The association between BPA exposure dosage and boys' anogenital distance. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

further divided the exposure into high and low categories based on the median of their estimated TWA_8 levels during the index pregnancy. The TWA_8 measurement appeared to be a reasonably good measure of actual BPA exposure. Using current TWA_8 against current urine BPA level, we found that among the exposed women, TWA_8 category high and low based on the median TWA_8 as the cutoff corresponded to geometric mean (95% CI) of urine BPA level of 33.0 (15.1–72.3; n = 8) and 10.8 μg/g Cr (3.7–31.5; n=10), respectively, supporting the use of TWA_8 as a reasonable measure for classifying BPA exposure level.

DISCUSSION

Although these findings need to be confirmed by other studies, this study provides important epidemiologic evidence that parental exposure to high levels of BPA during pregnancy could be associated with shortened AGD in male offspring. The relationship showed a dose-response fashion with increasing maternal BPA exposure levels in pregnancy associated with a higher likelihood of shortened AGD in male offspring.

Several animal studies reported decreased AGD after in utero exposure to BPA, with more consistent results in male than female offspring. Timing of AGD measurement ranged from at birth (Kim et al., 2001), to 4 days after birth (Murray et al., 2007), and to 113 days after birth (Ema et al., 2001). These findings from animal studies provide support for our results that maternal BPA exposure during pregnancy was associated with decreased AGD of male offspring, and such an association can be detected in newborns and older children.

Published human studies examining the effect of BPA on reproduction are still rare. We have reported previously that men's sexual function decreased after exposure to BPA (Li et al., 2010a, 2010b) and exposure to BPA also led to poor semen quality (Li et al., 2011). Although the health effect of in utero exposure to BPA on the development of the fetal reproductive organs in humans is largely unknown, the effect of in utero exposure to other endocrine-disrupting chemicals has been reported. Decreased AGD was found to be associated with in utero exposure to phthalates, an antiandrogenic agent, in a study of 134 male infants aged 2 to 36 months (Swan et al., 2005). In another study, increased maternal blood level of DDE in the first trimester was also found to be correlated with decreased anal position index, defined as the ratio of AGD to the distance between the coccyx and the scrotum (Torres-Sanchez et al., 2008), whereas the correlation between DDE and AGD was not found in another study using postnatal rather than prenatal maternal blood for the DDE examination (Longnecker et al., 2007). In the present study, we provide new evidence that in utero exposure to BPA was associated with a decreased AGD.

Development of the perineum and the external genitalia is determined by dihydrotestosterone, resulting in a greater AGD in males than in females. The most rapid development of AGD occurs during a masculinization programming window (MPW). The MPW is the time when sexual differentiation happens, during which androgen plays an essential role in directing mammalian sexual differentiation of the male phenotype. Exposure to chemicals with estrogen or antiandrogen properties dur-

ing the MPW can lead to maldevelopment of the male sexual organs, leading to shortened AGD, hypospadias, cryptorchidism, and altered penile length (Bowman et al., 2003; Hsieh, 2008; Welsh et al., 2008). BPA's endocrine disrupting property makes it a highly potent chemical to interrupt the development occurring in MPW. The MPW has been shown to occur during the 14th to 19th days of gestation in rats, corresponding approximately to the 8th to 14th weeks of gestation in human pregnancy (Welsh et al., 2008, 2010; Wolf et al., 2004).

Animal studies showed that there is little or no placental barrier to BPA (Nishikawa et al., 2010; Takahashi and Oishi, 2000). In human studies, a positive correlation has been found between maternal blood and umbilical cord blood BPA level in a study of 300 woman-fetus pairs (Lee et al., 2008). Thus, maternal exposure to BPA can readily lead to fetal exposure, providing biologic plausibility for the possible adverse effects of BPA on offspring through maternal exposure. In the present study, the average urine BPA level among exposed mothers (direct maternal exposure) was much higher than in unexposed parents. Combined with the fact that all mothers in the exposed group worked for at least 3 months during pregnancy (mostly the first 3 months of gestation, which is during the MPW), it is conceivable that all offspring in this group had relatively high levels of in utero BPA exposure. For the spouses of exposed fathers, although not exposed to BPA in the workplace directly, they were likely to have higher BPA exposure levels than women in the unexposed group, through indirect exposure to contaminated clothing, visits to the spouses' factories (BPA exposure in workplace), and residing in the vicinity of the factories. Through the in-person interviews, we found that 45% of exposed fathers did not routinely change their uniforms before discharge. Most of them (64%) did not routinely take a shower before going home. In addition, 19% of spouses of exposed male workers visited their husbands factories regularly at work. Finally, many workers' residences were close to the factories, a common practice in most parts of China. All these factors were likely to have led to a secondary exposure to BPA for female spouses of exposed fathers. Our urine assays of BPA levels confirmed that average urine BPA level was highest among women with direct BPA exposure in the workplace, followed by spouses of male exposed workers. The unexposed mothers (neither spouses were exposed to BPA in the workplace) had lowest urine BPA levels. This confirmation validated our exposure classification.

Human studies using AGD as the endpoint of interest have been reported either in babies (from newborn to <3 years) or adults (Thankamony et al., 2009; Eisenberg et al., 2011; Mendiola et al., 2011). Our finding provides additional support that AGD may be a useful and sensitive measure for endocrine-disrupting effects. AGD measure was well tolerated by all subjects and was quick to perform, with acceptable intraexaminer reliability. Moreover, in male rodents, shortened AGD persists into adulthood (Hotchkiss et al., 2004). In humans, AGD at birth was reported to be associated with subsequent AGD at 2 years of age (Thankamony et al., 2009). All these findings suggest the potential to use AGD as a biomarker to examine developmental antiandrogen effects. Its association with reproductive endpoints, including semen quality and testicular cancer, also makes it a valuable measurement of an early biomarker with both public health and clinical significance (Gray et al., 1999; Eisenberg et al., 2011; Mendiola et al., 2011).

The present study was limited by the small sample size and relatively low participation rates. The most common reason for boys' inability to participate in the study was that they were at school far from home, and the proportion of unavailable boys was similar between the exposed and unexposed groups. As a result, there is a reduced likelihood that the association between BPA exposure and AGD could be explained by their participation. In addition, our finding of a dose-response relationship provides some support for the validity of the observed association.

Because of the retrospective nature of the study, estimated TWA_8 was used to determine the exposure dosage during the index pregnancy, instead of maternal urine BPA level. We did not use current maternal urine BPA level as a substitute for BPA level during pregnancy, because the exposure levels have changed since the index pregnancy as a result of a change in job title, environmental BPA level, and the use of protective devices. Although we have demonstrated that current TWA_8 is highly correlated with current urine BPA, the association between BPA exposure and AGD could be effected because of inaccurate classification of BPA exposure category. However, because TWA_8 was generated before the AGD measurement in the present study, and thus not related to AGD, this misclassification would be nondifferential, and the effect of such misclassification, if it existed, would have attenuated the observed association.

CONCLUSION

These results need to be replicated in other studies, but our findings provide new evidence that in utero exposure to BPA may have an adverse effect on the reproductive system in male offspring, indicating a potentially disturbing interference of BPA with the development of fetal reproductive systems.

ACKNOWLEDGMENTS

We thank Roxana Odouli for her help in developing data collection instruments and preparing the manuscript and the participating factories for their cooperation.

REFERENCES

Thankamony A, Ong KK, Dunger DB, et al. 2009. Anogenital distance from birth to 2 years: a population study. Environ Health Perspect 117:1786–1790.

Bowman CJ, Barlow NJ, Turner KJ, et al. 2003. Effects of in utero exposure to finasteride on androgen-dependent reproductive development in the male rat. Toxicol Sci 74:393–406.

Calafat AM, Ye X, Wong LY, et al. 2008. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. Environ Health Perspect 116:39–44.

Carwile JL, Luu HT, Bassett LS, et al. 2009. Polycarbonate bottle use and urinary bisphenol A concentrations. Environ Health Perspect 117:1368–1372.

Eisenberg ML, Hsieh MH, Walters RC, et al. 2011. The relationship between anogenital distance,fatherhood, and fertility in adult men. PLoS One 6:e18793.

Ema M, Fujii S, Furukawa M, et al. 2001. Rat two-generation reproductive toxicity study of bisphenol A. Reprod Toxicol 15:505–523.

Foster PM, McIntyre BS. 2002. Endocrine active agents: implications of adverse and non-adverse changes. Toxicol Pathol 30:59–65.

Gray LE Jr, Wolf C, Lambright C, et al. 1999. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione,

chlozolinate, p,p′-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. Toxicol Ind Health 15:94–118.

Gupta C. 2000. Reproductive malformation of the male offspring following maternal exposure to estrogenic chemicals. Proc Soc Exp Biol Med 224:61–68.

He Y, Miao M, Herrinton LJ, et al. 2009a. Bisphenol A levels in blood and urine in a Chinese population and the personal factors affecting the levels. Environ Res 109:629–633.

He Y, Miao M, Wu C, et al. 2009b. Occupational exposure levels of bisphenol A among Chinese workers. J Occup Health 51:432–436.

Hotchkiss AK, Parks-Saldutti LG, Ostby JS, et al. 2004. A mixture of the ''anti-androgens'' linuron and butyl benzyl phthalate alters sexual differentiation of the male rat in a cumulative fashion. Biol Reprod 71:1852–1861.

Howdeshell KL, Furr J, Lambright CR, et al. 2008. Gestational and lactational exposure to ethinyl estradiol, but not bisphenol A, decreases androgen-dependent reproductive organ weights and epididymal sperm abundance in the male long evans hooded rat. Toxicol Sci 102:371–382.

Hsieh MH, Breyer BN, Eisenberg ML, Baskin LS. 2008. Associations among hypospadias, cryptorchidism, anogenital distance, and endocrine disruption. Curr Urol Rep 9:137–142.

Kim JC, Shin HC, Cha SW, et al. 2001. Evaluation of developmental toxicity in rats exposed to the environmental estrogen bisphenol A during pregnancy. Life Sci 69:2611–2625.

Kobayashi K, Miyagawa M, Wang RS, et al. 2002. Effects of in utero and lactational exposure to bisphenol A on somatic growth and anogenital distance in F1 rat offspring. Ind Health 40:375–381.

Le HH, Carlson EM, Chua JP, et al. 2008. Bisphenol A is released from polycarbonate drinking bottles and mimics the neurotoxic actions of estrogen in developing cerebellar neurons. Toxicol Lett 176:149–156.

Lee YJ, Ryu HY, Kim HK, et al. 2008. Maternal and fetal exposure to bisphenol A in Korea. Reprod Toxicol 25:413–419.

Li DK, Zhou Z, Miao M, et al. 2010a. Relationship between urine bisphenol-A level and declining male sexual function. J Androl 31:500–506.

Li DK, Zhou Z, Qing D, et al. 2010b. Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction. Hum Reprod 25:519–527.

Li DK, Zhou Z, Miao M, et al. 2011. Urine Bisphenol-A level in relation to semen quality. Fertil Steril 95:625–630.

Longnecker MP, Gladen BC, Cupul-Uicab LA, et al. 2007. In utero exposure to the antiandrogen 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) in relation to anogenital distance in male newborns from Chiapas, México Am J Epidemiol 165:1015–1022.

Mendiola J, Stahlhut RW, Jørgensen N, Liu F, Swan SH. 2011. Shorter anogenital distance predicts poorer semen quality in young men in Rochester, New York. Environ Health Perspect Mar 1. Epub ahead of print.

Monteilh C, Kieszak S, Flanders WD, et al. 2011. Timing of maturation and predictors of Tanner stage transitions in boys enrolled in a contemporary British cohort. Paediatr Perinat Epidemiol 25:75–87.

Murray TJ, Maffini MV, Ucci AA, et al. 2007. Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. Reprod Toxicol 23:383–390.

Nishikawa M, Iwano H, Yanagisawa R, et al. 2010. Placental transfer of conjugated bisphenol A and subsequent reactivation in the rat fetus. Environ Health Perspect 118:1196–1203.

Romano-Riquer SP, Hernandez-Avila M, Gladen BC, et al. 2007. Reliability and determinants of anogenital distance and penis dimensions in male newborns from Chiapas, Mexico. Paediatr Perinat Epidemiol 21:219–228.

Schonfelder G, Wittfoht W, Hopp H, et al. 2002. Parent bisphenol A accumulation in the human maternal-fetal-placental unit. Environ Health Perspect 110:A703–A707.

Swan SH, Main KM, Liu F, et al. 2005. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect 113:1056–1061.

Takahashi O, Oishi S. 2000. Disposition of orally administered 2,2-Bis(4-hydroxyphenyl)propane (Bisphenol A) in pregnant rats and the placental transfer to fetuses. Environ Health Perspect 108:931–935.

Tomova A, Deepinder F, Robeva R, et al. 2010. Growth and development of male external genitalia: a cross-sectional study of 6200 males aged 0 to 19 years. Arch Pediatr Adolesc Med 164:1152–1157.

Torres-Sanchez L, Zepeda M, Cebrian ME, et al. 2008. Dichlorodiphenyldichloroethylene exposure during the first trimester of pregnancy alters the anal position in male infants. Ann N Y Acad Sci 1140:155–162.

vom Saal FS, Hughes C. 2005. An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. Environ Health Perspect 113:926–933.

Welsh M, Saunders PT, Fisken M, et al. 2008. Identification in rats of a programming window for reproductive tract masculinization, disruption of which leads to hypospadias and cryptorchidism. J Clin Invest 118:1479–1490.

Welsh M, Macleod DJ, Walker M, et al. 2010. Critical androgen-sensitive periods of rat penis and clitoris development. Int J Androl 33:e144–e152.

Wetherill YB, Akingbemi BT, Kanno J, et al. 2007. In vitro molecular mechanisms of bisphenol A action. Reprod Toxicol 24:178–198.

Wolf CJ, LeBlanc GA, Gray LE, et al. 2004. Interactive effects of vinclozolin and testosterone propionate on pregnancy and sexual differentiation of the male and female SD rat. Toxicol Sci 78:135–143.