FINAL REPORT

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Institution to which award was made:	Kaiser Foundation Research Institute, a Division of Kaiser Foundation Hospitals 1800 Harrison Street, 16th Floor Oakland, CA 94612-3433 510/625-3431
Project Title:	Exposure to Bisphenol A & Reproductive Effect in Humans
KP Project Numbers:	Cost Center 115-9327; KFRI Short Title CN-01DLi-01-H
Co-Investigators:	Harvey Checkoway, PhD Ersheng Gao, MD Lisa Herrinton, PhD Noah Seixas, PhD Jintao Wang, MD Shouzheng Xue, MD, MPH Wei Yuan, MD, PhD Zhijun Zhou, MD, PhD
Project Director:	De-Kun Li, MD, PhD
Sponsors:	Centers for Disease Control and Prevention (CDC) National Institute for Occupational Safety and Health (NIOSH)
Grant Number:	5R01OH007580-05
Start & End Dates:	Project Period: 9/30/2003 – 9/29/2011
Final Report Completed:	February 8, 2012

Abstract (500 words or less)

To examine the health effects of exposure to bisphenol-A (BPA) in the human population, we conducted an occupational cohort study in several regions in China where occupational exposure to BPA existed. The exposed group consisted of workers who were exposed to BPA in the workplace. The unexposed cohort consisted of workers similar to the exposed workers in the same locations, but without exposure to BPA in the workplace. A total of 1,937 subjects including workers, their spouses and their children, if any, participated in the study. BPA exposure was measured both through workplace monitoring (for the exposed workers) and biomarker assays (urine and blood specimens). We examined the impact of BPA exposures on the male reproductive system (semen quality and sexual dysfunction), female pregnancy outcomes (shortened anogenital distance and decreased birth weight), and hormone profiles. After controlling for other confounding factors, we observed the following findings:

1. High urine BPA level in male participants is associated with lower sperm quality.

2. Exposure to high BPA level increases the risk of male sexual dysfunction.

3. Female exposure to high BPA during pregnancy is associated with a shortened anogenital distance (AGD) in male offspring, an indication of increased risk of genital anomaly.

4. Female exposure to high BPA during pregnancy is associated with decreased birth weight among offspring.

These findings provide the first piece of epidemiological evidence from human studies demonstrating that high BPA exposure level presents a detrimental effect to human health, especially to the reproductive systems in this case. The observed BPA adverse effect on both male and female reproductive systems is consistent with the findings from animal studies. Our findings have filled the knowledge gap due to a lack of human studies and provide important information for the scientific community and regulatory agencies when evaluating the safety of BPA exposure in the workplace and the general environment.

Significant (Key) Findings

The results from the funded study have led to significant findings that have made important contributions to the understanding of bisphenol-A (BPA) health effect for the scientific community and regulatory agencies including **the *FDA*s from the US and other countries, US *EPA* and *WHO***. Many findings from the six publications resulting from this study have been widely reported by the news media worldwide. The key findings from the study so far include:

1. High urine BPA level in male participants is associated with lower sperm quality.

2. Exposure to high BPA level increases the risk of male sexual dysfunction.

3. Female exposure to high BPA during pregnancy is associated with a shortened anogenital distance (AGD) in male offspring, an indication of increased risk of genital anomaly.

4. Female exposure to high BPA during pregnancy is associated with decreased birth weight among offspring.

Translation of Findings.

All of the above findings are the first epidemiological evidence from the human population to demonstrate adverse health effects of BPA exposure in the workplace. In addition to providing the scientific community and regulatory agencies with new evidence of adverse BPA health effects, these findings point to the need to reduce BPA exposure in workplaces to protect male workers from BPA damage to their reproductive system (sexual dysfunction and low semen quality). Female workers also need to be protected from high BPA exposure, especially during pregnancy, to prevent potential adverse impact on their fetuses.

Outcomes/ Impact.

Before our study, there was evidence of adverse BPA health effects from animal studies, but not from human studies. Findings from our study have provided the first pieces of epidemiological evidence from a human population that confirmed the findings from animal studies and indeed demonstrated adverse BPA effects on the male reproductive system and fetal development if BPA exposure occurred during pregnancy. Given the sparsity of BPA studies in human populations, these findings have provided valuable information for scientists and regulatory agencies to assess BPA health effects, thus, establishing safety guidelines and regulations in the near future.

The Final Progress Report

BACKGROUND

Similar to diethylstilbestrol (DES), bisphenol-A (BPA) was first recognized in the 1930's as a potential synthetic estrogen. However, unlike DES that was eventually selected for medicinal use and later discovered to be a carcinogen and to cause many other health problems, 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. Use of polycarbonate bottles has been shown to lead to increased urine BPA levels. Most human populations could be constantly exposed to some levels of BPA. In a national sample of the U.S. population, more than 90% of spot urine samples had detectable BPA with a median urine level of 2.7 μg/L. Since BPA has a fast rate of metabolism (half-life time < 6 hours), this finding suggests a continuous exposure to BPA in the U.S. population. Similar findings of BPA exposure have been reported in other countries as well.

Animal studies have shown that BPA affects the male reproductive system including androgen receptors, male sex hormone levels, male reproductive organs including testes, epididymis, sperm and seminal vesicles, the prostate gland, and sperm production. Changes in sexual behavior including reduced performance in latency and frequency of intromission among rodents that had been exposed to BPA have also been reported. BPA has been shown to have both estrogenic and antiandrogenic effects in both *in-vivo* and *in-vitro* studies.

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 U.S. government panels convened by the National Toxicology Program and the National Institute of Environmental Health and Safety, respectively.

We have conducted an occupational cohort study to evaluate whether exposure to high levels of BPA affects the male reproductive system including semen quality and sexual dysfunction. We also examined whether female BPA exposure during pregnancy had any adverse impacts on offspring.

SPECIFIC AIMS

1. Among men (both exposed workers and spouses of female exposed workers), is there a relationship of exposure with sex hormone profile (including testosterone, androstenedione, FSH, inhibin B, and estradiol), semen quality (sperm concentration, morphology, and motility), and frequency of sexual intercourse?

As described above, we have published three papers which showed an adverse effect of BPA exposure in the workplace on poor semen quality and male sexual dysfunction.

BPA effect on male hormones is being examined and analyzed at the present time.

2. Among the children of exposed workers, is there a relationship of parental exposure with sex ratio, birthweight, age at development of secondary sex characteristics, menstrual characteristics, and sex hormone profile (including testosterone, androstenedione, estradiol, progesterone, FSH, LH, and inhibin B)?

As described above, we have published two papers showing that female exposure to high BPA levels during pregnancy increases the risk of a shortened anogenital distance (AGD) in male offspring, an indication of genital anomaly and decreased birth weight.

The BPA effect on hormone levels is still being analyzed.

3. Among women (both exposed workers and spouses of male exposed workers), is there a relationship of exposure with sex hormone profile (including estradiol, progesterone, follicle-stimulating hormone [FSH], and luteinizing hormone [LH]), menstrual disorders, frequency of sexual intercourse, time-to-pregnancy, and spontaneous abortion?

Information on these variables has been collected as planned including pregnancy history and sex hormone profiles. The data are still being analyzed. More in-depth analyses on the BPA effect on the female reproductive system are yet to be conducted.

METHODS

From 2004-2008, 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.

A total of 1,937 participants were recruited into the study including workers, their spouses and their children, if any. BPA exposure was ascertained in multiple ways. (1) An exposure matrix based on occupational history and past exposure. (2) Current exposure level in the workplace based on air sample collection through personal monitoring. And (3) measurement of biomarkers based on urine and blood specimens.

We ascertained multiple outcomes to examine the BPA health effects. For male participants, we collected semen specimens and information on sexual function. For female participants, we asked about their reproductive history. For both male and female participants, we collected blood specimens to analyze hormone profiles.

We analyzed the data using multiple logistic regression (for dichotomized outcomes) and linear regression (for continuous outcomes) to control for confounders.

RESULTS

After controlling for other factors, we found:

1. High urine BPA level in men is associated with lower sperm quality with a statistically significant dose-response relationship.

2. Exposure to high BPA level increases the risk of male sexual dysfunction with 4-7 fold increased risk compared to unexposed controls.

3. Female exposure to high BPA during pregnancy is associated with a shortened anogenital distance (AGD) in male offspring, an indication of increased risk of genital anomaly.

4. Female exposure to high BPA during pregnancy is associated with decreased birth weight among offspring.

DISCUSSION

Among the strengths of the study, the most important one is the consistency of the findings. Among the six parameters measuring semen quality, all of them were inversely associated with urine BPA exposure level: the higher the urine BPA level, the worse were the semen parameters, although volume and morphology did not reach statistical significance. Among the seven parameters measuring sexual dysfunction, all of them were inversely related to BPA exposure. The associations of BPA exposure with poor semen quality and sexual dysfunction themselves are consistent given that semen quality and sexual function are both parameters of the male reproductive system. For female BPA exposure during pregnancy, the adverse effects on the male genital organ and decreased birth weight are consistent with the effect of *in-utero* BPA exposure. The observed BPA effect on both male and female

workers is also consistent with the findings from animal studies. Such consistency enhances the validity of our findings.

CONCLUSIONS

Findings from this study provide the first epidemiological evidence from human populations that BPA exposure in the workplace has adverse effects on the adult male reproductive system and fetal development.

PUBLICATIONS

Six publications resulting from the study so far are:

Li DK, Zhou Z, Qing D, He Y, Wu T, Miao M, Wang J, Weng X, Ferber JR, Herrinton LJ, Zhu Q, Gao E, Checkoway H, Yuan W (2010a) 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, He Y, Qing D, Wu T, Wang J, Weng X, Ferber J, Herrinton L, Zhu Q, Gao E, Yuan W (2010b) Relationship between Urine Bisphenol-A (BPA) Level and Declining Male Sexual Function. J Androl 31:500-506

Li DK, Zhou Z, Miao M, He Y, Wang J, Ferber J, Herrinton LJ, Gao E, Yuan W (2011) Urine bisphenol-A (BPA) level in relation to semen quality. Fertil Steril 95:625-630

Miao M, Yuan W, He Y, Zhou Z, Wang J, Gao E, Li G, Li DK (2011a) In utero exposure to bisphenol-A and anogenital distance of male offspring. Birth Defects Res A Clin Mol Teratol 91:867-872

Miao M, Yuan W, Zhu G, He X, Li DK (2011b) In utero exposure to bisphenol-A and its effect on birth weight of offspring. Reprod Toxicol 32:64-68

He Y, Miao M, Herrinton LJ, Wu C, Yuan W, Zhou Z, Li DK (2009) Bisphenol A levels in blood and urine in a Chinese population and the personal factors affecting the levels. Environ Res 109:629-633

Program Director/Principal Investigator (Last, First, Middle): Li, De-Kun

Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: Exposure to Bisphenol A & Reproductive Effects in Humans

Total Enrollment: 1,937 **Protocol Number:**

Grant Number: NIOSH (115-9327)

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

Ethnic Category	Females	Males	Sex/Gender Unknown or Not Reported	Total
Hispanic or Latino	0	0	0	0 **
Not Hispanic or Latino	849	1,088	0	1,937
Unknown (individuals not reporting ethnicity)	0	0	0	0
Ethnic Category: Total of All Subjects*	849	1,088	0	1,937 *
Racial Categories				
American Indian/Alaska Native	0	0	0	0
Asian	849	1,088	0	1,937
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	0	0	0	0
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	**0**	0
Racial Categories: Total of All Subjects*	849	1,088	0	1,937 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	Females	Males	Sex/Gender Unknown or Not Reported	Total
American Indian or Alaska Native	0	0	0	0
Asian	**0**	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	**0**
Black or African American	0	0	0	0
White	0	0	0	0
More Than One Race	0	0	0	0
Unknown or Not Reported	0	0	0	0
Racial Categories: Total of Hispanics or Latinos**	0	0	0	0 **

* These totals must agree.
** These totals must agree.

FINANCIAL STATUS REPORT

(Short Form)

(Follow instructions on the back)

1. Federal Agency and Organizational Element to Which Report is Submitted	2. Federal Grant or Other Identifying Number Assigned By Federal Agency	OMB Approval No.	Page of
AHRQ	**R01 OH007580-05**	**0348-0038**	pages

3. Recipient Organization (Name and complete address, including ZIP code)

Kaiser Foundation Research Institute, a Div of Kaiser Foundation Hospitals,1800 Harrison St., 16th Floor, Oakland, CA 94612

4. Employer Identification Number	5. Recipient Account Number or Identifying Number	6. Final Report	7. Basis
94-1105628	**115-9327**	■ Yes ☐ No	☐ Cash ☑ Accrual

8. Funding/Grant Period *(See instructions)* From: (Month, Day, Year)	To: (Month, Day, Year)	9. Period Covered by this Report From: (Month, Day, Year)	To: (Month, Day, Year)
09/30/2003	**09/29/2011**	**09/30/2010**	**09/29/2011**

10. Transactions:	I Previously Reported	II This Period	III Cumulative
a. Total outlays	1,205,421.27	235,105.58	1,440,526.85
b. Recipient share of outlays			0.00
c. Federal share of outlays	1,205,421.27	235,105.58	1,440,526.85
d. Total unliquidated obligations			**0.00**
e. Recipient share of unliquidated obligations			**0.00**
f. Federal share of unliquidated obligations			**0.00**
g. Total Federal share *(Sum of lines c and f)*			1,440,526.85
h. Total Federal funds authorized for this funding period			1,443,452.00
i. Unobligated balance of Federal funds *(Line h minus line g)*			2,925.15

11. Indirect Expense	a. Type of Rate *(Place "X" in appropriate box)*			
	☑ Provisional	☐ Predetermined	☐ Final	☐ Fixed
	b. Rate	c. Base	d. Total Amount	e. Federal Share
	56.00%	**-2,277.81**	**-$1,275.57**	**-1,275.57**

12. *Remarks: Attach any explanations deemed necessary or information required by Federal sponsoring agency in compliance with governing legislation.*

13. Certification: **I certify to the best of my knowledge and belief that this report is correct and complete and that all outlays and unliquidated obligations are for the purposes set forth in the award documents.**

Typed or Printed Name and Title	Telephone (Area code, number and extension)
Stanley Watson, Vice President and Director	**(510) 625-4724**
Signature of Authorized Certifying Official	Date Report Submitted
S B Watson	**December 21, 2011**

FINANCIAL STATUS REPORT

(Short Form)

PLEASE DO NOT RETURN YOUR COMPLETED FORM TO THE OFFICE OF MANAGEMENT AND BUDGET. SEND IT TO THE ADDRESS PROVIDED BY THE SPONSORING AGENCY.

Please type or print legibly. The following general instructions explain how to use the form itself. You may need additional information to complete certain items correctly, or to decide whether a specific item is applicable to this award. Usually, such information will be found in the Federal agency's grant regulations or in the terms and conditions of the award. You may also contact the Federal agency directly.

Item	Entry	Item	Entry

1, 2 and 3. Self-explanatory.

4. Enter the Employer Identification Number (EIN) assigned by the U.S. Internal Revenue Service.

5. Space reserved for an account number or other identifying number assigned by the recipient.

6. Check *yes* only if this is the last report for the period shown in item 8.

7. Self-explanatory.

8. Unless you have received other instructions from the awarding agency, enter the beginning and ending dates of the current funding period. If this is a multi-year program, the Federal agency might require cumulative reporting through consecutive funding periods. In that case, enter the beginning and ending dates of the grant period, and in the rest of these instructions, substitute the term "grant period" for "funding period."

9. Self-explanatory.

10. The purpose of columns I, II, and III is to show the effect of this reporting period's transactions on cumulative financial status. The amounts entered in column I will normally be the same as those in column III of the previous report in *the same funding period*. If this is the first or only report of the funding period, leave columns I and II blank. If you need to adjust amounts entered on previous reports, footnote the column I entry on this report and attach an explanation.

10a. Enter total program outlays less any rebates, refunds, or other credits. For reports prepared on a cash basis, outlays are the sum of actual cash disbursements for direct costs for goods and services, the amount of indirect expense charged, the value of in-kind contributions applied, and the amount of cash advances and payments made to subrecipients. For reports prepared on an accrual basis, outlays are the sum of actual cash disbursements for direct charges for goods and services, the amount of indirect expense incurred, the value of in-kind contributions applied, and the net increase or decrease in the amounts owed by the recipient for goods and other property received, for services performed by employees, contractors, subgrantees and other payees, and other amounts becoming owed under programs for which no current services or performances are required, such as annuities, insurance claims, and other benefit payments.

10b. Self-explanatory.

10c. Self-explanatory.

10d. Enter the total amount of unliquidated obligations, including unliquidated obligations to subgrantees and contractors.

Unliquidated obligations on a cash basis are obligations incurred, but not yet paid. On an accrual basis, they are obligations incurred, but for which an outlay has not yet been recorded.

Do not include any amounts on line 10d that have been included on lines 10a, b, or c.

On the final report, line 10d must be zero.

10e. f, g, h, h and i. Self-explanatory.

11a. Self-explanatory.

11b. Enter the indirect cost rate in effect during the reporting period.

11c. Enter the amount of the base against which the rate was applied.

11d. Enter the total amount of indirect costs charged during the report period.

11e. Enter the Federal share of the amount in 11d.

Note: If more than one rate was in effect during the period shown in item 8, attach a schedule showing the bases against which the different rates were applied, the respective rates, the calendar periods they were in effect, amounts of indirect expense charged to the project, and the Federal share of indirect expense charged to the project to date.

*U. S. Government Printing Office: 1993 - 342-197/81289

Form Approved Through 06/30/2012
OMB No. 0925-0001

Department of Health and Human Services **Final Invention Statement and Certification** *(For Grant or Award)*	DHHS Grant or Award No. 5R01OH007580-05

A. We hereby certify that, to the best of our knowledge and belief, all inventions are listed below which were conceived and/or first actually reduced to practice during the course of work under the above-referenced DHHS grant or award for the period

9/30/03 *original effective date* through 9/29/11 *date of termination*.

B. Inventions (Note: If no inventions have been made under the grant or award, insert the word *"NONE"* under Title below.)

NAME OF INVENTOR	TITLE OF INVENTION	DATE REPORTED TO DHHS
	NONE	
(Use continuation sheet if necessary)		

C. Signature — This block ***must*** be signed by an official authorized to sign on behalf of the institution.

Title	Name and Mailing Address of Institution
Executive Director, Financial Op's and Comp	Kaiser Foundation Research Institute, a Division of Kaiser Foundation Hospitals 1800 Harrison Street, 16th Floor Oakland, CA 94612-3433
Typed Name Willard D Donnelly	
Signature: Willard D Donnelly — Date: 12/24/2011	

HHS 568 (Rev. 06/09)

CDC Procurement & Grants Office - Branch V
Equipment Inventory Listing

Report Date:	2/8/12	Grant Number:	5R01OH007580-05
Project Title:	Exposure to Bisphenol A...	Project Period:	9/30/03 - 9/29/11
Grantee Name:	Kaiser Fndtn Research Inst.	Project Officer:	Joan Karr
Grants Management Officer:	Stanley Watson	Grants Specialist:	Maryann P. Monroe

Description of Item: i.e. pH Meter	Mfr.[1] i.e. Fischer	Serial Number	Quantity	Condition[2]	Location[3]	Purchase Cost	Date Received [mm/dd/yyyy]
None.							

[1]Mfr. (Manufacturer)
[2]Condition: (Excellent) (Good) (Fair) (Poor) (Inoperable)
[3]Location: complete physical address

For Government Use Only, not to be completed by the Grantee
Property Administrator & PO Disposition Recommendation and Instructions:

Description of Item	Disposition[1]	Address[2]
[Copy from above]	_____Transfer Title _____Retain and Compensate Awarding Agency _____ Return to Program Office _____Other (explain)	Attn: [Project Officer] CDC / NIOSH 1600 Clifton Road, NE MS E-74 Atlanta, GA 30329-4018
[Copy from above]	_____Transfer Title _____Retain and Compensate Awarding Agency _____ Return to Program Office _____Other (explain)	

[1]Check the appropriate disposition
[2]CDC Warehouse is the central receiving point for delivery of all non-hazardous and non-perishable supplies and equipment, CDC –AM–2004-03, update 2010