Final Performance Report

Petrochemical Exposures and Reproductive Outcomes

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Significant Findings

A series of studies were conducted during 1994-1998 to investigate the association between petrochemical exposures and reproductive outcomes. The studies included different groups of female employees in a large petrochemical corporation located in Beijing, China

In a retrospective study of 2853 women aged 20-44 who had experienced a pregnancy, 57% of the women reported occupational exposure to petrochemicals during the first trimester of their pregnancy. There was a significantly increased risk of spontaneous abortion for women working in all of the production plants with frequent exposure to petrochemicals (8.8%) compared with those working in nonchemical plants (2.2%). Based on job history, the overall odds ratio (OR) for spontaneous abortion associated with petrochemical exposure was 2.7 (95% confidence interval [95% CI] 1.8 to 3.9) after adjusting for potential confounders. In analyses for exposure to specific chemicals, a significantly increased risk of spontaneous abortion was found with exposure to benzene (OR 2.5; 95% CI 1.7 to 3.7), gasoline (OR 1.8; 95% CI 1.1 to 2.9), and hydrogen sulfide (OR 2.3; 95% CI 1.2 to 4.4).

A cross-sectional analysis on menstrual patterns was performed in 3343 women, largely overlapping those in the above study. Years of exposure to benzene were calculated from the current and previous two jobs, based on the information obtained from an interview questionnaire. Average menstrual cycle length was also asked for each woman. After accounting for various confounders, having long (>35 days) or short (<21 days) menstrual cycles was associated with the number of years exposed to benzene. The nature of the relationship appeared nonlinear, with the increase becoming distinct after 7 years. The adjusted odds ratio for a long or short cycle was 1.7 (95% CI 1.3 to 2.3) for each additional 5 years of benzene exposure, among women with exposure longer than 7 years.

Another cross-sectional study was conducted to evaluate the association between menstrual patterns and organic solvent exposure in a different group of 1408 women. The subjects included 1070 newlyweds and 338 first-pregnancy planners. Average menstrual cycle length was asked for the previous year. Based on the petrochemical production process in the plants, each workshop was classified as exposed or nonexposed for aromatic solvents: benzene, toluene, xylene, and styrene. Working in a workshop exposed to any of the four solvents was associated with a slight increase in the risk of a long cycle (>35 days) (OR 1.3, 95% CI 0.9 to 1.9). Compared to a nonexposed workshop, working in an exposed workshop longer than 5 years was associated with an OR of 1.7 (95% CI 1.0 to 2.8), whereas working in an exposed workshop for 5 years or less did not show a distinct increase in the odds of a long cycle (OR 1.0, 95% CI 0.6 to 1.7).

A group of 279 women planning to conceive were followed prospectively for a study of the effect of organic solvents on fecundability. Daily morning urine samples and menstrual diaries were collected. A conception was identified by a rise in urine hCG for three or more days above the level obtained from sterilized control women. An exposure index was developed for benzene according to a standardized industrial hygiene evaluation. Each woman was assigned to an exposure category: none, low, or high. Compared to women with no exposure to benzene, women with high exposure showed a reduced fecundability (fecundability ratio 0.5, 95% CI 0.2 to 0.9) after adjusting for various confounders. Women with low exposure showed a smaller and nonsignificant reduction (fecundability ratio 0.8, 95% CI 0.5 to 1.4).

During 1994-1998, a total of 1237 employees in the petrochemical corporation delivered a baby in an affiliated workers' hospital. A study was conducted in these women to investigate the effect of petrochemical exposure on birth weight. According to industrial hygiene evaluation of each woman's job title and workshop, exposure status was categorized as none, exposure to benzene, or exposure to solvents other than benzene. After adjusting for gestational age and other confounders, exposure to benzene was associated with 62g reduction in birth weight (p=0.05) compared to no exposure.

Exposure to solvents other than benzene was associated with 58g reduction in birth weight (p=0.05).

A methological study was conducted to develop strategies for exposure assessment in complex working environment such as a petrochemical industry. A subset of 132 women was selected from the participants in the prospective study of fecundabillity described above. Quantitative exposure assessment was preformed for organic solvents by personal air sampling. The workers' time-weighted average exposures to benzene, toluene, styrene and xylene were 0.11 ppm, 0.04 ppm, 0.03 ppm, and 0.02 ppm, respectively. The peak exposure during short-term handling of solvents were 1.22 ppm, 0.19 ppm, 0.15 ppm and 0.06 ppm, respectively, on average among the workers. The maximum of the peak exposure to benzene, toluene, styrene and xylene was 74.3 ppm, 2.7 ppm, 2.0 ppm and 0.7 ppm, respectively.

The validity of self-assessed exposure status was compared with professional assessment by an industrial hygienist and with assessment by actual measurement. There was a fair agreement between workers' self-report and measurement or professional assessment on benzene and styrene exposure, but a poor agreement was found on toluene and xylene. The agreement was better with a check list, compared to an open ended question.

A simulation study was conducted to investigate the effects of exposure measurement error on the estimation of odds ratios when there is a time window of susceptibility. This issue is of concern when the exposure profiles are likely to be unevenly distributed because of the accident-like events ("unscheduled events") resulting in peak exposures. The results demonstrated that when there is a critical time window, the use of cumulative dose can obscure a hypothetical "true" odds ratio of 3 to 1. The factors influence the odds ratio the most were the size of the critical time windows, the geometric means of the unscheduled events, and the threshold of the exposure.

Usefulness of Findings

The findings of the studies show that petrochemical exposures, especially benzene and other organic solvents, are associated with various adverse reproductive outcomes, such as spontaneous abortion, menstrual disturbance, reduced fertility, and reduced birth weight. These effects were observed among female workers in a modern petrochemical industry, where the exposure levels were well controlled at or below the current OSHA PEL's. Therefore, the results imply that the current standard may not be appropriate for employees who are pregnant or planning to conceive.

For accurate evaluation of reproductive risks, assessment of organic solvent exposure needs to take into account peak exposures, as well as time-weighted averages. The risk may be underestimated by using cumulative exposure as an exposure index for the reproductive endpoints that involve a susceptible time window.

Abstract

During 1994-1998, we have conducted a series of occupational epidemiologic studies to investigate the association of exposure to benzene and other organic solvents with adverse reproductive outcomes in a large petrochemical corporation in Beijing, China. A retrospective study found that the risk of spontaneous abortion was associated with exposure to benzene, gasoline, and hydrogen sulfide. Cross-sectional studies in two separate groups of women observed similar trend of increased frequency of prolonged menstrual cycles with longer years of exposure to organic solvents. In a prospective follow-up of women planning to conceive, benzene exposure was associated with reduced fecundability after adjusting for other solvents and potential confounders. In a study of birth outcomes who delivered a baby during the study period, exposure to benzene and other solvents were associated with a statistically significant reduction of birth weight adjusting for gestational age and other confounders. Although the levels of exposures were below the limit regulated by OSHA and recommended by NIOSH, our studies show that even low-level occupational exposure to benzene and other organic solvents is linked to a broad spectrum of adverse reproductive outcomes including menstrual disorders, spontaneous abortion, birth weight and decreased fecundability. These results suggest that the exposures need to be more strictly monitored among employees who are pregnant or planning to conceive.

Background of the Project

Adverse reproductive outcomes are significant public health concerns. In humans, only one-fourth to one-third of fertilized eggs are likely to survive to term (Witschi et al, 1970). Although definite statistics are unavailable, experts estimate that with roughly 3 million live births per year in the United States, there are approximately 600,000 spontaneous abortions, 24,000 fetal deaths, 30,000 neonatal deaths, and 150,000 live-born children with congenital anomalies (Rudolph et al, 1986). Prior to the third month of clinically confirmed pregnancy, about three-fourths of spontaneous abortions show chromosomal or other abnormalities. However, the cause of most spontaneous abortions is unknown, as is the cause of 60 to 70% of birth defects (Karkinen-Jaaskelainen, 1985).

An estimated 8.4 percent of U.S. couples in which the wife is of childbearing age are infertile. In some cases this inability to bear children appears to correct itself; in other cases the infertility persists. The causes of infertility are also unknown in a high proportion of cases.

There has been an increasing awareness of the potential for occupational and environmental exposures to hazardous substances to adversely affect reproductive outcome in both males and females. As women enter the labor force in ever greater numbers, clinicians are more frequently asked to assess the potential effect of work on the pregnancy outcome of their patients. Estimates of the proportion of U.S. women who were employed during their pregnancies indicate that, in 1980, 63.2 percent of married women over 20 years of age who had delivered a live infant were employed at some time during the 12 months prior to the birth of their children. Of these women, an estimated 17 percent, or 314,000 mothers, worked in industries and occupations in which they faced possible exposure to 10 potential teratogen.

The scientific literature from human epidemiologic studies on reproductive health hazards, for the most part, are inconclusive because of methodological problems. In a recent review (Rosenberg et al, 1987), several common weaknesses were identified, including inadequate sample size, inappropriate control groups, inadequate attention to potentially confounding factors, poor characterization of exposures, low response rates, and potential for recall and selection biases. Although these problems may not have occurred in every study, their frequency indicates the magnitude of the task faced by all researches in this field. It was recommended that development and use of standard methods in future studies is an important strategy to address these problems. Many reproductive endpoints (e.g. spontaneous abortion) are difficult to measure. The concepts, methods, and problems of measuring spontaneous abortion risk have been reviewed recently (Modvig, 1990). The problems touched on include the process of pregnancy verification, the changes in risk by gestational age and maternal age, and the presence of induced abortions. The authors conclude that no study design used so far appropriately measures the total risk of spontaneous abortion from early conception to the end of the 27th week.

For many years the occurrence of early pregnancy loss could only be inferred from indirect evidence. The recent, improved and more specific biochemical assays that measure the sequence of amino acids unique to the beta subunit of the pregnancy hormone human chorionic gonadotropin (hCG) molecule, have allowed detection of pregnancy within a few days of implantation. Among women trying to conceive, β-hCG was detected on average at 25.4 days from the first day of last menstrual period (LMP) (Wilcox et al, 1985). Several epidemiologic studies (Wilcox et al, 1985, 1988) have been conducted using the more specific assays. One of the largest studies (Wilcox et al, 1988) included 221 North Carolina women who were attempting to conceive, who were followed over 707 menstrual cycles. 198

pregnancies were identified by an increase in the hCG level near the expected time of implantation. Of these, 22 percent ended before pregnancy was detected clinically. The total rate of pregnancy loss after implantation was 31 percent. All of the participants were volunteers, and they may not have been representative of the general population. At the present time, the rates of subclinical and/or early pregnancy loss have not been estimated from a representative sample in any community or any specific occupational group. The possible association between risk of early pregnancy loss and maternal characteristics or exposures was also examined among these same 221 North Carolina women (Wilcox et al, 1990). These factors included a women's age, pregnancy history, weight, education, prenatal DES exposure, cigarette smoking, use of caffeinated or alcohol beverage. None of them was definitely associated with early pregnancy loss. Because the sample size was small, the possibility of undetected real effects cannot be excluded, and further study, therefore, is required (Wilcox et al. 1990).

In recent years, attention has focused on organic solvents as potential reproductive toxins. This increased attention results from both animal evidence of reproductive effects and anecdotal reports of clusters. These organic solvents include benzene, toluene and related compounds.

Benzene is an important industrial chemical, a petroleum by-product, a component of unleaded gas, and thus a ubiquitous environmental pollutant (Collegium Ramazzini Int. Conf. on Benzene, 1985). Total U.S. production in 1985 was 9.73 billion tons. NIOSH has estimated that close to 2 million U.S. workers have a potential for benzene exposure. However, few studies have examined its effects on reproductive health outcomes. Because benzene has an appreciable vapor pressure at ambient temperature, hazardous occupational exposure usually occurs via inhalation. In addition, benzene can also be taken up by ingestion in food or in water and can be absorbed through the skin.

Data on reproductive effects included in the 1983 results of the National Toxicology Program Bioassay have indicated a dose-response relationship between benzene exposure and preneoplastic response in reproductive tissues (Davis et al, 1986). Menstrual disturbances and heavy bleeding have been observed in women exposed to benzene, and women appear to be more susceptible to benzene exposure than men. Benzene crosses the placenta and is present in fetal blood in amounts equal to or greater than levels in maternal blood. In experimental animals, benzene may alter ovarian function, and cause reduced body weight, and skeletal variants at doses below those which cause acute toxicity (Barlow et al, 1982). A Finnish study has indicated a possible association of benzene exposure with spontaneous abortions in rubber industry workers (Davis, 1986). Additional experimental animal and epidemiologic studies of benzene exposure have been recommended.

Alkylbenzenes are another major group aromatic hydrocarbons of toxicological interest. The major products to which humans are likely to be exposed include toluene, xylene, ethylbenzene and cumene. These compounds are primarily derived from petroleum distillation and coke oven effluent. The National Academy of Sciences reported that in 1980 the U.S. production of alkylbenzene was 6.4, 3.7, 3.9 and 1.8 millions of metric tons respectively for toluene, xylene, ethylbenzene and cumene. NIOSH estimates that 4.8 million workers in the USA are potentially exposed to toluene, the fourth largest number for an individual chemical. The NIOSH estimate for xylene exposure is 140,000 workers. The mixtures of these compounds may account for levels as high as 38 percent of unleaded gasoline. The potential for human exposure, albeit often at low levels, is accordingly expanded beyond industrial workers to gasoline station workers and the general public at large. It is, therefore, necessary to have a full understanding of the potential effects of these compounds (Andrews, 1991).

Toluene was found to be fetotoxic in animals, causing birth-weight reduction. Xylene has not been teratogenic in animal studies but has been associated with minor skeletal anomalies consistent with

fetal toxicity, and with possible preimplantation losses after exposure in very early pregnancy (Barlow et al, 1982). No epidemiologic studies of reproductive outcomes in workers with exposure to toluene and/or xylene have been conducted which confirm or deny these findings.

Styrene is widely used as a solvent. NIOSH estimates that at least 30,000 workers in 1000 plants are potentially exposed in the United States to styrene, and more than 300,000 workers are potentially exposed to compounds containing styrene. Inhalation exposure of the rat to styrene appears to alter gonadotrophic function and estrous cycles at levels of exposure, just below those which cause overt toxicity (Barlow et al, 1982). An increase in the incidence of spontaneous abortion has also been found to be associated with styrene exposure (Hemminki et al, 1980).

The combined effects of these solvents is also of current interest. Mixed-function oxidases have a broad specificity, one solvent may compete with another for available catalytic sites. Thus toluene has been shown to be a competitive inhibitor of the metabolism of benzene (Andrews et al, 1977). Benzene plus toluene was found to cause less weight retardation of fetuses than benzene alone. The mixture of benzene and toluene caused a higher incidence of extra ribs than toluene alone. The mixture also caused increased postimplantation loss of fetuses.

Despite a growing body of information concerning reproductive health hazards and the risk they pose, what is known about reproductive health hazards is far outweighed by what is unknown. Most commercial chemicals have not been thoroughly evaluated for their possible toxic effects on reproduction and development. There is uncertainty as to which specific agents are harmful because workers are often exposed to more than one hazardous agent in the workplace, or there may be synergism among a number of factors (including non-occupational factors) that cause reproductive impairment. Much of the information on suspected reproductive health hazards is derived from animal studies, making extrapolation to humans difficult. There may be a substantial time lag between cause and effect. Consequently, there are no reliable estimates as yet of the basic measures of reproductive risk in the workplace--the number of workers exposed to such hazards, their levels of exposure, and the toxicity of the agents to which they are exposed. Because of these unknowns, the management of uncertainty is the central issue in the protection of the reproductive health and the procreative capacity of working men and women.

This study investigated reprospectively and prospectively the association between petrochemical exposures, particularly aromatic organic solvents, and reproductive outcomes in a large cohort of oil refinery workers. A sensitive and accurate biomarker of pregnancy, the β-hCG, was used to identify conception in the prospective study of women planning to conceive. Clinical spontaneous abortion and birth outcomes were studied among a larger group of female employees.

Specific Aims

The principal goal of this project is to assess the effects of occupational exposure to aromatic solvents on women's reproductive health by enrolling and following a cohort of reproductive age women who work at Beijing Yanshan Petrochemical Corporation (BYPC). An "unexposed" cohort will be drawn from comparable workers without direct exposure to those chemicals. The following specific hypotheses will be addressed:

a. Occupational exposure of women workers to benzene, toluene, and styrene in BYPC is associated with adverse reproductive outcomes. The end points include menstrual problems, time taken to conceive, spontaneous abortion, prematurity and low birthweight.

b. There is an exposure-response relationship between chronic and acute (peak) exposure to benzene, toluene, and styrene and the risk of adverse reproductive outcome.

c. Exposure to those chemicals before conception and during each trimester of pregnancy is associated with different adverse reproductive outcomes, i.e. earlier exposure is likely to affect fecundity and spontaneous abortion, while later exposure may result in prematurity and low birthweight.

d. There is an interactive effect of benzene and toluene on reproductive outcomes.

e. Adverse reproductive outcomes are also associated with personal factors including active and passive smoking, indoor coal combustion, cooking oil fumes, alcohol consumption, diet, use of herbal medicines, heavy lifting, body position during work, rotating shiftwork, and physical activities outside workplace. To the degree detectable, these personal factors will be accounted for confounders in the testing of hypothesis a, b, c and d.

f. In addition to evaluating the above hypotheses, methodological aspects were investigated to improve exposure assessment in future epidemiologic studies among petrochemical workers.

Procedures

Overview of study population and design

This study compares reproductive outcomes between women workers who have a history of exposure to aromatic organic solvents (benzene, toluene, xylene and styrene) and those without such a history of exposure, at Beijing Yanshan Petrochemical Corporation (BYPC). BYPC, located in a southwest suburb of Beijing, has been in operation since 1969. This complex represents a very large integrated set of petroleum and chemical processing operations in 17 major different production plants and institutes. It currently employs 47,000 workers and staff members, of whom 39,539 are production workers (24,490 men and 15,049 women). According to the inventory of the complex as of the year 1993, a total of 7,166 workers have been exposed to petro-chemical hazards. Selection procedures are described in detail in the following sections for each component of the study. Briefly, we identified 3070 married women who had experienced at least one pregnancy for a retrospective study of spontaneous abortion and menstrual cycle pattern. We also enrolled another group of 1,510 newlywed women for a cross-sectional study of menstrual cycle pattern. Among those, a total of 357 women were followed up for a

prospective study of time to pregnancy and early pregnancy loss. Finally, we recruited 1237 female employees who gave birth to a baby during the study period. These multiple enrollment procedures of the study were conducted in an integrated process (Figure 1). In addition, a group of 60 sterilized women was recruited at the start of the study to provide daily urine samples for three cycles. Levels of hCG measured from sterilized women's urine samples served as a baseline value to identify a conception in the prospective study component.

Structure of the prospective component of the study

We utilized the unique aspects of Chinese family planning system which mandates every couple who plans to get married receive a marriage health exam and family planning consultation at designated health centers. At the time they wish to have a baby, they are required to obtain childbirth permission from district family planning office. In our study base, a woman became eligible for the prospective study upon receipt of permission to have a child. The follow-up schedule is shown in Figure 2. A baseline survey of all the enrolled women and their husbands was conducted at a local research office. Those not attending the research office were seen in their homes. A standardized questionnaire used in ongoing historical cohort study will be administered by trained interviewers to collect information about reproductive history, a detailed history of occupational exposure of these women and their spouses, demographic characteristics and potential confounding variables such as active and passive smoking, indoor coal combustion, cooking oil fumes, alcohol consumption, diet, use of herbal medicines, heavy lifting, body position during work, rotating shiftwork, and physical activities outside workplace. Weight and height were measured by standard methods.

In addition to providing baseline information on menstrual histories, subjects provided daily morning urine specimens for 12 months, or until a pregnancy has been confirmed clinically. All samples were collected by the subjects in 20 ml double-seal vials provided by the investigators. Subjects delivered their vials daily to one of several refrigerators provided at the workplace. Samples were then transported to the laboratory, aliquoted and stored at -20 °C. Samples were assayed for hCG to determine "early pregnancy loss" and fecundity. In addition, each woman was requested to keep a diary for her menstrual period, symptoms, sexual activity, general health status, medication, cigarettes smoking, alcohol consumption, diet and physical activity.

If a woman reported a missed or late period, or early signs/symptoms of pregnancy, she was instructed to go to the designated hospital for a clinical check-up and a lab assay of human chorionic gonadotropin (hCG) in urine. Once a woman was confirmed to be pregnant, she received regular prenatal care, delivery services and postnatal care, and was followed by staff at the designated hospital. For normal pregnancies, clinical visits were scheduled according to standard clinical guidelines. For complicated pregnancies, clinical visits were scheduled as needed. At each visit, length of gestation, blood pressure, weight gain, fundal height, pregnancy complications, medications, lab tests and examinations, and pregnancy outcomes were recorded. Detailed information on changes of jobs, working hours, occupational exposures, active and passive smoking status, diet, sources of indoor air pollutants, average time spent for daily transportation and household work were obtained. If a woman gave a live birth, the newborn's sex, gestational age, birth weight, and crown to heel length were recorded. During the daily follow-up period, one work day was randomly chosen for each subject for an exposure assessment including detailed job activity analysis and personal air sampling **(Appendix I-1).**

Field procedures

Preparation, recruitment and organization

The study was approved by the institutional review boards of Harvard School of Public Health and Beijing Medical University. A two-day workshop was held with the local investigators to explain the aims, procedures and significance of the study. Methods for maintaining confidentiality and the voluntary nature of the study was also explained. The clinic directors, the family planning coordinators and the interviewers attended the workshop. The logistical issues concerning subject identification, recruitment, data collection, sample storage, transportation and analysis, and data input were fully discussed and the appropriate arrangement was made during the workshop. All the potential eligible female subjects were sent a letter inviting them to participate in the study. Included in the letter was a specific explanation of the aims, procedures and significance of the study, confidentiality, and the voluntary nature of the study.

Baseline survey

A baseline survey of all the enrolled female subjects was conducted at a central office. The arrangement will be made by the workshop supervisors and the coordinators at a time that was convenient for the subject. During the visit, the interviewer first asked the subject to read and sign an informed consent statement. After enrollment, interviewers administered a previously validated questionnaire to the subject to collect baseline information on reproductive health, socio-demographic, environmental, and personal covariates (**Appendix I-2**).

Diary and urine sample collection

All subjects were asked to complete daily diaries and collect daily urine samples during the follow-up period. A **beginning questionnaire** was administered to update the information on important covariates and changes in environment, job and health since the initial baseline survey.

Diary. The diary was completed by the subject every day and typically took about five minutes to complete. Completed diaries were sealed and turned in to the family planning coordinator daily. The interviewer reviewed all the completed diaries weekly and personally discussed, maintaining confidentiality at all times, any discrepancies found or answer any questions the subject had. The **missing diary card** was completed in case of missing daily diaries for more than three consecutive days to document the reasons for the missingness.

Urine. Urine samples were collected daily. The **urine collection registration card** was used to record the urine collection and transportation information and were filed by the family planning coordinator. Each subject was given a 250 ml beaker for collecting urine and a 50 ml double-sealed vial for storing and transferring the urine. Each vial was labeled with a bar code for the subject ID, weekday and date. The subject was instructed to void into the beaker upon awakening each day, to pour 50 ml of the urine into the double-sealed vial, to place the vial into a plastic bag and to temporarily store it in her home refrigerator. Subjects brought their filled vials to the workshop daily and the family planning coordinator at each workshop was responsible for collecting urine samples and diaries from each subject and storing them in the refrigerator at the plant's clinic. During weekends or holidays, the coordinators visited each household to collect the urine samples. During the follow-up, if the subject travels outside of Yanshan for business or vacation, we only requested to record daily diary. Fortunately, over 90% of the participants did not have to travel outside of Yanshan

for more than three consecutive days during the study period.

All collected specimens were then transported, by the interviewers, to the hospital. After adequate shaking, two aliquot samples were placed into 5 ml vials by a trained laboratory technician, which had the same bar code as the 50 ml double-sealed vial, and stored at -20°C. One sample was shipped, by ground transportation (~1.2 hours) on dry ice, to BMU Center for Ecogenetics and Reproductive Health for analysis. Another sample was stored at BYPC for two purposes: (1) as a backup for the current urinary assays, and (2) for future research.

Termination and drop out

A brief **termination questionnaire** was administered when the subject terminates collection of daily urine samples and completion of the diaries. Special attention was paid to those subjects who leave the study, as they may represent a susceptible subgroup to benzene toxicity. For each drop out, the field coordinators completed a **drop-out questionnaire** to determine the subject's reason for leaving the study.

Data Collection Instruments

The **baseline interview and the beginning questionnaire** **(Appendix I-2 and I-3)** consisted predominantly of close-ended and some open-ended questions regarding socio-demographic characteristics (date and place of birth, ethnicity, educational level, job training and residence), current use of prescription and non-prescription medications or herbal remedies, history of chronic illness, sleep disorders, reproductive history (age at menarche, usual menstrual cycle characteristics, contraceptive use, pregnancy history, previous spontaneous and induced abortion, history of infertility, and history of gynecological disorders or surgery), years of employment, job title and category, salary grades, activities and duration of the previous and current job, work shifts, ergonomic aspects of workplace activities, job-related stress, operation of machinery and tools which involve dust or chemicals (including solvents, metals, fumes, gases and acids), exposure to radiation, noise or heat, source of social support, physical activities outside the workplace, time spent watching TV, active and passive smoking, indoor coal combustion, cooking oil fumes, type and location of cooking stove, home use of air conditioner, current consumption of tea, coffee and alcohol, diet, and lifestyle.

A one-page **daily diary** **(Appendix I-4)** consisted of an ID number and work-related and non-work-related questions. The non-work-related questions obtain information on: daily urine collection, menstrual bleeding, premenstrual symptoms, use of prescribed and non-prescribed medications, any illnesses, frequency of sexual intercourse, contraceptive use, active and passive smoking, indoor air pollution, alcohol use, water consumption, amount of vigorous exercise and physical activity, emotional upset, and any unusual events or accidents. The work-related questions obtain information on: type of shift, hours worked, amount of time spent at each body position during work, temperature and humidity in the workshop, changes in job and exposures, and any unusual events or accidents. On the back of the diary, the subjects were requested to record detailed information on the event and subject's activity including nature, time, duration, distance from the emission source and use of protective equipment.

A brief **termination questionnaire** **(Appendix I-5)** was administered to female subjects when they terminate collection of daily urine samples and completion of the diaries. It contains questions about the reason for terminating the diary, last date of diary entry, last menstrual period and any associated symptoms. In addition, we have included questions designed to check the validity of several daily diary

questions.

The **missing diary card** **(Appendix I-6)** was completed whenever a subject has failed to make recordings in the daily diary for more than three consecutive days. This card indicated the reason for the missing diary entries, whether the subject has had any vaginal bleeding with or without any accompanying symptoms, and whether she had sexual intercourse without using contraception during the missing period. The research staff at each plant reviewed the daily diary cards at least once a week to determine the need for missing diary cards. The missing diary cards were collected and filed for each subject until she terminated the daily diary and urine collection.

The **urine collection registration card** **(Appendix I-7)** was designed to serve as a record for the urine collection and transportation information to be filed by the family planning coordinator. The information in the card includes the date, the name of the subject, the time and the person who received the urine sample, and the time and the person who took the sample to the plant general hospital where the urine samples are to be aliquoted and stored by a trained technician.

The **drop out questionnaire** **(Appendix I-8)** was designed to record the reasons for those subjects who withdraw from the study.

Specific Reproductive Outcomes

I. Association of petrochemical exposure with spontaneous abortion

(Published in Occupational Environmental Medicine 1998;55:31-36. See attached reprint.)

Methods

Plant employment records identified 3105 women who were married, were 20-44 years of age, and had never smoked. Of those, 3070 women (98.8%) reported at least one pregnancy. From this group, 2853 (95%) of the women participated in the study. According to their plant employment record, about 57% of these women workers reported occupational exposure to petrochemicals during the first trimester of their pregnancy. Trained interviewers administered a standardized questionnaire to this group of women and their husbands, collecting information on reproductive history, pregnancy outcomes, employment history, occupational exposure, smoking habits, alcohol consumption, indoor air pollution, and demographic variables. The results from the womens' first pregnancies were analyzed.

Results

There was a significantly increased risk of spontaneous abortion for women working in all of the production plants with frequent exposure to petrochemicals (8.8%; range of 5.8%-9.8%) compared with those working in nonchemical plants (2.2%; range of 0.0%-7.1%). Also, when a comparison was made between exposed and non-exposed groups within each plant, exposure to petrochemicals was consistently associated with an increased risk of spontaneous abortion. The overall odds ratio (OR) was 2.7 (95% confidence interval (95% CI)1.8 to 3.9) after adjusting for potential confounders. When the analysis was performed with the exposure information obtained from the women's interview responses for (self reported) exposures, the estimated OR for spontaneous abortions was 2.9 (95% CI 2.0 to 4.0). The analysis was repeated by excluding those 452 women who provided inconsistent reports between recalled exposure and work history, and a comparable risk of spontaneous abortion (OR 2.9; 95% CI 2.0 to 4.4) was found. In analyses for exposure to specific chemicals, an increased risk of spontaneous abortion was found with exposure to most chemicals, and the results for benzene (OR 2.5; 95% CI 1.7 to 3.7), gasoline (OR 1.8; 95%CI 1.1 to 2.9), and hydrogen sulphide (OR 2.3; 95% CI 1.2 to 4.4) were significant.

Conclusion

An increased risk of spontaneous abortion was found associated with the exposure to petrochemicals, including benzene, gasoline, and hydrogen sulphide.

II. Petrochemical exposure, ergonomic factors and menstrual disturbances

Methods

The details of the study design have been described previously (Xu, 1998. See attached reprint.). Standardized questionnaires were administered to 3434 married women aged 20 to 44 who worked in one of the plants in the petrochemical corporation under study. We defined long cycle or oligomenorrhea to be an average cycle length of more than 35 days, and short cycle or polymenorrhea to be an average cycle length of 20 days or less. Abnormal menstrual cycle length was defined as a long or short cycle.

Workers in the petrochemical company, especially those in the oil refinery or chemical plants, were potentially exposed to several different chemical hazards including benzene, gasoline, manganese, acid, lime dust, hydrogen sulfide, ammonia, and toluene. Using questionnaire responses, we coded years exposed to a particular chemical as the number of years continuously exposed to the chemical, up to and including the present time. To do this we used information from questions about specific chemical exposures for the current and previous two jobs. If a woman reported exposure to a particular chemical in her job, it was assumed that she had been exposed to that chemical throughout that job. Specifically, years exposed to a particular chemical was coded as 0 if the woman was not exposed to that chemical in her job. The sum of years employed in the job exposed to the chemical was defined as the exposure years. Information on various potential confounders was collected by the questionnaire.

Logistic regression was used to model the relationship between the occurrence of abnormal menstrual cycle length, and years exposed to benzene, adjusting for potential confounders. Generalized additive models using a loess smooth was used to examine the relationship between exposure years and the probability of abnormal menstrual cycle length. This was done using S-plus software.

Results

Prevalence of long cycle and short cycle was 7.0% and 2.9% respectively. The nature of the relationship between years exposed to benzene and the predicted probability of abnormal cycle length suggested that the probability appeared to increase after the first 7 years of exposure. We fit a model with a piecewise linear regression model for years exposed to benzene, allowing for one slope for the first 7 years of exposure, and a different slope for more than 7 years of exposure. The slopes were significantly different for these two time periods (p=.015). After accounting for perceived stress, adverse working conditions such as long hours of standing, and individual factors such as age, the predicted probability of having abnormal menstrual cycle length increased with number of years exposed to benzene, for exposure of more than 7 years. After 7 years of benzene exposure, every additional 5 years of exposure resulted in an estimated adjusted odds ratio of having abnormal cycle length of 1.71 (95% CI 1.27 to 2.31) (Table 1). Feeling stressed at work was an imprtant predictor in this model. Perceived stress was itself highly correlated with adverse working conditions, particularly with exposure to loud noise and frequent lifting.

Conclusion

This study suggests a significant association of exposure to benzene with menstrual disturbance.

Table 1. Odds ratios for the probability of having an abnormal menstrual cycle length as a function of individual factors, adverse working conditions, and benzene exposure among female workers aged 20-44 in a large petrochemical plant in Beijing, China.

		Odds ratio (95% CI)			
	multiplier*	Unadjusted		Adjusted	
Benzene exposure ≤ 7 yrs	5	0.85	(0.61, 1.19)	0.79	(0.55, 1.13)
Benzene exposure > 7 yrs	5	1.61	(1.22, 2.14)	1.71	(1.27, 2.31)
Age	5	0.97	(0.86, 1.10)	0.88	(0.77, 1.01)
Body Mass Index	5	1.23	(1.03, 1.47)	1.27	(1.05, 1.53)
Non-chemical plant		1.00	(referent)	1.00	(referent)
Oil Refinery		1.40	(1.05, 1.87)	1.31	(0.96, 1.78)
Chemical plant I		0.99	(0.71, 1.38)	0.93	(0.66, 1.32)
Other chemical		1.09	(0.80, 1.48)	1.04	(0.76, 1.44)
Perceived Stress	1	1.19	(1.01, 1.41)	1.21	(1.02, 1.42)

* The multiplier column indicates the number of units of increase in the covariate for which the odds ratio is given.

III. Effect of exposure to organic solvents on menstrual cycle length

Methods

Study population

As discussed earlier, the Chinese health care system mandates that every couple planning to marry must visit a designated, district health center where they will receive a *marriage health examination* (MHE) and participate in family planning counseling. When a couple plans to attempt to conceive a child, they are required to obtain *childbirth permission* (CBP) from the local family planning office. We exploited these requirements of the health care system to identify newlywed women, ages 20 to 40 years who work in the petrochemical industry, to participate in a prospective reproductive health study of the effects of exposure to organic solvents. The recruited potential enrollees from the Yanshan Petrochemical Corporation, in Beijing, China (BYPC), from 1994 to 1998. BYPC is a large petroleum and chemical processing plant made up of 17 different but well integrated production plants and institutes. As of 1998 the corporation employs approximately 39,000 production workers and approximately 40% are women. A total of 1,510 women were enrolled of which 1134 (75%) were identified by MHE's. Those who were identified by both a MHE and CBP were classified as CBP enrollees. Women having prior marriages, had experienced a pregnancy, or had a medically diagnosed gynecological or endocrine disease were ineligible. Participation rate was greater than 95% among eligible women. A structured questionnaire was administered by a trained interviewer to all eligible participants to collect information on menstrual patterns, occupational exposures, and various potential confounders. There were only 3 active smokers and another 4 subjects were missing information on smoking. These 7 subjects were excluded from this study. In addition, 95 subjects were missing either menstrual information or current employment information. Therefore, a total of 1,408 subjects were left for the analyses. This study was approved by the institutional review boards of Harvard School of Public Health and Beijing Medical University.

Assessment of exposures

After enrollment, a detailed assessment of work exposure to petrochemicals was obtained by interview using a specialized questionnaire developed by a industrial hygienist familiar with the petrochemical process at BYPC. Included in the assessment was information on; plant name, workshop name, job title, work process, checklist of materials the workers handled, types and levels of chemicals and dusts in the work environment, and use of personal protective measures. Information on non-chemical exposures were also obtained including; shift-work, noise, vibration, perceived stress, and ergonomic exposures such as lifting, standing, physical exertion.

The assessment of exposure to solvents was based on the evaluation of the workshops in which the individuals worked. The petrochemical industry involves a complex integrated system composed of well-defined unit processes. Each unit process reflects a set of chemical conversions which starts with raw materials and ends with product materials. These unit processes involve specific equipments that are physically located in a certain section of the plant. Division of workshops represent such unit processes. BYPC is comprised of 17 different plants each having a variable number of workshops. Overall, there are a total of 218 workshops, each of which represents a single unit process. We have conducted a methodological research on exposure assessment and developed a database for workshop evaluation. For a chemical workshop, for example, the database includes a process map, a brief description of the unit process, a list of job tasks, and a list of chemicals involved in the workshop as raw material, product material, impurities, and background exposure. The full list of chemicals

included 55 that has been suspected as a reproductive toxin.
Based on the information in the workshop database, each workshop was qualitatively classified by the expert hygienist as "exposed" versus "unexposed" for benzene, toluene, styrene, and xylene, respectively. "Exposed" category indicates that there is possibility of exposure to the chemical in the workshop, and "unexposed" category indicates that exposure to the chemical is unlikely in the particular workshop. This workshop evaluation was combined with the name of the workshop in which individual worker was working, resulting in the exposure status of each woman to each solvent. Women who had exposure to any of the four solvents were categorized as "exposure to any solvent". We also examined "years of exposure", in the current workshop, to each organic solvent as a continuous variable to investigate potential dose-response relationships. Thirty-two subjects reported having worked in more than one workshop. These workshops were also evaluated for organic solvent exposure as outlined above and added into their years of exposure.

Assessment of Menstrual Patterns

Menstrual patterns were assessed using an interviewer administered questionnaire. In addition to collecting a detailed reproductive history from each women, menstrual information for the past year was collected. This included questions regarding average cycle length, longest and shortest cycle length, and average duration of bleeding. Based on the usual definitions of menstrual cycle length disorder, we defined a *prolonged menstrual cycle or oligomenorrhea* as an average cycle length of greater than 35 days. This definition also includes amenorrhea, which is usually defined as a menstrual cycle lasting longer than 90 days. A *short menstrual cycle or polymenorrhea* was defined as an average cycle length of 21 days or less. *Prolonged bleeding duration or menorrhagia* was defined as an average menstrual bleeding period longer then 7 days.

Potential confounders

In addition to information on reproductive history and menstrual patterns, detailed information was collected on various potential confounders. These included; age, body weight and height, date of marriage, current and past contraceptive use, past pregnancy, active and passive smoking, indoor coal combustion, cooking oil fumes, alcohol consumption, diet, use of herbal medicines, heavy lifting, body position during work, rotating shift-work, perceived work stress based on 4 point scale ranging from 0-3, and physical activities outside the workplace.

Statistical Analysis

Menstrual pattern variables were coded as indicator variables where "1" indicated the presence and "0" the absence of the particular outcome variable. Exposure to solvents were similarly coded as binary. For nonexposed subjects, years of exposure was given 0. For the rest, years of exposure was treated. The low prevalence of short menstrual cycle (9/1408) and prolonged bleeding duration (20/1408) resulted in some categories of covariate status that contained no subjects leading to unreliable estimates of the effect of exposure status. Therefore, only unadjusted association of these outcomes with exposure variables are presented.

The presence of passive smoking was defined as having exposure to at least one active smoker either at home or in the workplace on a regular basis. Rotating shift-work was coded as 1 for 3- or 4-shift workers, and 0 for the rest. College education, perceived work stress, physical exertion or heavy lifting in usual work shifts were coded as indicator variables similar to the menstrual pattern variables. We explored for possible nonlinear relationships between the outcome variables and all continuous covariates using generalized additive models. Age and body mass index (BMI) did not indicate a departure from linearity. Therefore these variables were included in the models as continuous. Years of exposure to solvents also showed linear trend in general. However, there was some suggestion that the risk of prolonged cycle starts to increase around 3 years. Therefore, the effect

of "years of exposure to any solvents" was presented with the exposure both in continuous scale and in categories in the multivariate analysis.

Linear multiple logistic regression was used to estimate the effect of exposure variables adjusting for covariates. Model selection was carried out by first examining the full model including all the variables of interest. Covariates that did not change the association between the exposure and outcome and were not significant independent predictors were excluded from the final model. All analyses were carried out using either SAS or Splus.

Results

The prevalence of oligomenorrhea stratified by exposure status is presented in Table 2 Among 138 subjects who had prolonged menstrucl cycle, 6 subjects had amenorrhea (menstrual cycle length > 90 days). Since few subjects were exposed to only one of the four aromatic organic solvents studied (benzene, toluene, xylene, and styrene), mutually exclusive categories were formed from several different combinations. Among the 15 (= 2^4 - 1) possible categories from different combination of four chemicals, only the ones shown in the Table 1 had any subject in the category, and those with no subject were left out of the table. There was higher prevalence of oligomenorrhea among those subjects exposed to any aromatic solvent compared to those who were unexposed.

Table 3compares the prevalence rate of oligomenorrhea between exposed and unexposed group for each stratum of potential confounders. Higher rates were observed in the exposed group consistently across the strata of nearly all confounders examined. Older age, higher BMI, passive smoking, perceived work stress, and lifting work showed a higher percentage of long menstrual cycles. CBP (child birth permission) cohort had a higher frequency of long cycles. This cohort is 2 years older on average than MHE (marriage health exam) cohort. In addition, CBP cohort included more subjects from the chemical processing plants compared to non-chemical plants.

In Table 4 results from multivariate logistic regression are presented. Odds ratios for prolonged menstrual cycle associated with exposure variables were shown. The odds ratios were adjusted for age, BMI, enrollment cohort, and passive smoking. Exposure variables were presented in different forms. Any aromatic solvent exposure indicated an increased risk of prolonged menstrual cycle, both in MHE and CBP cohort. Adjusted odds ratios were calculated for each of the solvents, benzene, toluene, styrene, and xylene. All of them indicated an increased risk of prolonged menstrual cycle, with xylene showing the greatest. The exposure-year distribution was skewed to the more years, 3 years being the 75th percentile, and 0 years (nonexposure) the median. Among the exposed group, 5 years was the median. One additional year's exposure to any solvent was associated with 6% (OR, 1.06) increase in the risk, if the effect is assumed to be continuous. This effect size implies that for an additional 3 years of exposure, there is 20% increase in the risk of prolonged cycle. If the exposure year is dichotomized at 75th percentile, i.e. 3 years, exposure to the solvents longer than 3 years was associated with an odds ratio of 1.4, compared to nonexposed group. Those with shorter exposure (< 3 years) did not show an increased risk of prolonged cycle length. Compared to nonexposed group, exposure longer than 5 years was associated with an OR of 1.7 (95% CI; 1.0, 2.8), whereas exposure of 5 years or less had an OR of 1.0 (95% CI; 0.6, 1.7).

There were 20 subjects with prolonged menstrual bleeding (12 nonexposed, 8 exposed), and the unadjusted OR associated with the exposure to any solvent was 1.48 (95%CI; 0.58, 3.6). Among 9 subjects with short menstrual cycle length, none belonged to the exposed group.

Table 2. Prevalence of oligomenorrhea (average cycle length >35 days) by solvent exposure category among newlywed women in Yanshan Petrochemical Corporation Beijing, China, 1994-1998.

Solvent Exposure	Frequency of Oligomenorrhea (%)	Total
None	**82 (8.5)**	**968**
Any aromatic solvent	**57 (12.9)**	**442**
Benzene only	4 (12.1)	33
Styrene only	0	3
Benzene+Toluene	4 (9.3)	43
Benzene+Styrene	6 (12.5)	48
Benzene+Toluene+Styrene	2 (6.9)	29
Benzene+Toluene+Xylene	8 (9.1)	88
Benzene+Toluene+Styrene+Xylene	32 (16.3)	196
Total	**138 (9.8)**	**1408**

Table 3. Prevalence of oligomenorrhea (average menstrual cycle length >35 days) among subjects within the categories of solvent exposure and potential risk factors. Newly married female workers in the Yanshan Petrochemical Corporation, Beijing, China, 1994-1998.

Variables		Prevalence of Oligomenorrhea					
		Unexposed		Exposed		Total	
		%	N	%	N	%	N
Age (tertiles)	20.0 - 23.6	6.5	355	9.1	121	7.1	476
	23.7 - 25.0	8.3	315	11.5	156	9.3	471
	25.0 - 34.5	11.1	298	16.6	163	13.0	461
BMI (tertiles)	14.8 - 20.3	6.4	326	5.6	144	6.2	470
	20.3 - 22.0	8.7	321	10.1	148	9.2	469
	22.0 - 36.7	10.3	319	22.3	148	14.1	467
College education	No	9.3	674	13.0	347	10.6	1021
	Yes	6.5	295	11.8	93	7.8	386
Passive smoking	No	6.6	469	10.4	231	7.9	700
	Yes	10.2	499	15.3	209	11.7	708
Cohort*	MHE	7.7	823	9.3	247	8.0	1070
	CBP	13.1	145	17.1	193	15.4	338
Rotating shift	No	8.3	749	15.5	194	9.8	943
	Yes	9.2	207	10.2	245	9.7	452
Work stress	No	8.3	884	13.7	410	10.0	1294
	Yes	11.3	71	0	29	8.0	100
Lifting	No	7.6	830	12.3	391	9.1	1221
	Yes	13.8	123	16.3	49	14.5	172
Total		**8.5**	**968**	**12.7**	**440**	**9.8**	**1408**

*MHE: enrolled at marriage health exam,
CBP: enrolled at childbirth permission

Table 4. Adjusted OR (odds ratio) and 95% CI (confidence interval) for oligomenorrhea (average cycle length > 35 days), associated with exposure variables. Newly married female employees in, Yanshan Petrochemical Corporation, Beijing, China, 1994-1998.

Exposure	OR*	95% CI
Any aromatic solvent	1.3	(0.9, 1.9)
MHE cohort	1.2	(0.7, 2.0)
CBP cohort	1.5	(0.8, 2.9)
Benzene	1.3	(0.9, 1.9)
Toluene	1.3	(0.9, 1.9)
Styrene	1.4	(0.9, 2.1)
Xylene	1.5	(1.0, 2.2)
Exposure years, any solvent	1.06	(0.99, 1.13)
Any solvent 0- 3 years, vs. None	0.7	(0.3, 1.6)
Any solvent > 3 years, vs. None	1.4	(1.0, 2.2)
Any solvent 0-5 years, vs. None	1.0	(0.6, 1.7)
Any solvent > 5 years, vs. None	1.7	(1.0, 2.8)

* Adjusted for age, BMI, enrollment cohort, and passive smoking

IV. Organic solvent exposure and reproductive endpoints: prospective study results

Methods

Assessment of exposure

Our power calculation showed that 150 subjects in exposed group nonexposed group, respectively, have 80% power. Therefore, we cagegorized the exposure status as "Nonexposed", "Benzene exposure", and "Exposed to other solvents", because benzene exposure was the most prevalent. Exposure to benzene or other solvents was determined by the industrial hygiene evaluation of individual women's information on job title, workshop, and plant name.

Definition of outcomes

Menstrual disorders

We defined a woman as having menstrual disorder if she reported a prolonged menstrual cycle (>35 days), shortened menstrual cycle (< 21 days), intermenstrual bleeding, irregular cycles (cycle length variation greater than 8 days).

Fecundability

The standard definition of fecundability is the probability of conception for one menstrual cycle. We used the following two measures of fedundability. Conception was defined as three or more days with urin hCG values > 0.60 ng/mL, based on the control values from sterilized women.

Time taken to conceive: The number of cycles from the time when a woman begins to have unprotected intercourse to the time of conception.

Fecundability ratio: the risk ratio for conception between exposure groups calculated from Cox proportional hazard model.

Fetal loss

Clinical spontaneous abortion: Clinically identified fetal death before 28 weeks of gestation

Early Fetal Loss: loss prior to 20 weeks gestation, identified by urinary hCG values.

Urinary Hormone Analysis

Creatinine measurement of all urine samples was carried out using the Jaffe method. Duplicates of each urine sample was placed side by side in the same microplate.

Assessment of EFL was determined by prospective evaluation of hCG in daily urine specimens using a highly specific and sensitive immunoradiometric assay (Columbia Combo IRMA). Briefly, the IRMA was developed by Dr. John O'Connor of Columbia University. The capture antibodies for this assay are

B109 and B204 and the detection antibody is an iodinated anti-β-hCG clone B108 (125I-B108). The profile of the hCG values in the negative control urine samples collected from a cohort of 60 ligated women will serve as the reference value to evaluate the subclinical pregnancy for the study subjects (Wilcox et al., 1988). The criterion for elevated hCG indicative of a subclinical miscarriage is three consecutive measurements of urinary hCG with values greater than the baseline values among the sterile women, so that criteria can achieve specificity close to 1.0 (Weinberg et al., 1992). Priority hCG analyses will be conducted on daily urine specimens of the entire menstrual cycle to assess early conception and early losses of pregnancy. A conception was defined as a hCG rise (0.6 ng/ml) for three or more consecutive days. EFL was defined as consecutive three samples of urinary hCG greater than baseline value among the sterile women, with a concurrent or subsequent menstruation. This definition was adapted from the algorithm by Wilcox (1988) and Weinberg (1992).

Results

Daily urinary hCG of 1,497 menstrual cycles from 357 women has been analyzed to define early pregnancy loss. The results suggest that exposure to benzene may be associated with increased risk of menstrual disorders, dysmenorrhea, decreased fecundability, and spontaneous abortion (clinical or sub-clinical; Table 5). Although the results did not reach statistical significance due to inadequate sample size, the findings from the prospective study is supported by the consistent results from cross-sectional and retrospective studies in this project.

Table 5. Results from BYPC prospective reproductive health study of women workers.

Environmental and epidemiologic information		Petrochemical exposure status			
		None	**Benzene**	**Others**	**Total**
Mean benzene concentration, ppm ± SD (n)		**.03±.04 (23)**	**.16±.44 (63)**	.07±.34 (32)	.11±.37 (118)
Number of woman subjects		71	182	104	357
Mean marriage age, yr±SD		24.0±1.6	24.0±2.4	24.1±2.6	24.1±2.5
Mean working period at enrollment, yr±SD		5.3±2.8	5.8±2.4	5.1±2.6	5.5±2.5
Number of cycles (number of days)		294(8,082)	732(22,255)	471(14,010)	1,497(44,347)
Available urinary hCG, days		5,395	14,203	8,840	28,438
Available daily diaries, days		7,226	19,565	12,370	39,165
Menstrual disorders (baseline)	Prevalence, %	21%	27%	21%	24%
	Odds ratio (95% CI)	1.0	**1.4 (.72-2.7)**	1.0 (.48-2.1)	
Dysmenorrhea (baseline)	Prevalence, %	44%	57%	51%	53%
	Odds ratio (95% CI)	1.0	**1.7 (1.0-3.0)**	1.3(.73-2.5)	
Menstrual disorders (follow-up)	Incidence, %	12%	17%	19%	17%
	Odds ratio (95% CI)	1.0	**1.4 (.86-2.3)**	1.5 (.91-2.6)	
Dysmenorrhea (follow-up)	Incidence, %	45%	54%	42%	48%
	Odds ratio (95% CI)	1.0	**1.4 (.81-2.4)**	.8(.45-1.5)	
Fecundability	Cycles, median (mean)	3 (4.6)	5(5.6)	4(4.9)	17%
	Risk ratio (95% CI)	1.0	**.83 (.56-1.2)**	.91 (.59-1.4)	
Clinical spontaneous abortion or EFL	Incidence, %	30%	47%	22%	36%
	Odds ratio (95% CI)	1.0	**2.1 (.68-6.3)**	.65(.18-2.3)	

V. Benzene exposure and time to conception: an application of urine hCG biomarker

Methods

Study population and design

The Chinese health care system mandates that when a married couple plans to attempt to conceive a child, they are required to obtain childbirth permission from the local family planning office. We exploited this requirement of the health care system to identify newlywed women, ages 20 to 40 years who work in the petrochemical industry, to participate in a prospective reproductive health study of the effects of exposure to benzene. We recruited potential enrollees from the Yanshan Petrochemical Corporation, in Beijing, China (BYPC), from 1994 to 1998. BYPC is a large petroleum and chemical processing plant made up of 17 different but well integrated production plants and institutes. As of 1998 the corporation employs approximately 39,000 production workers and approximately 40% are women. Women having prior marriages, had experienced a pregnancy, or had a medically diagnosed gynecological or endocrine disease were ineligible.

A structured questionnaire was administered by a trained interviewer to all eligible participants to collect information on reproductive history, occupational exposures, and various potential confounders. Each subject was then followed monthly by the field staffs in the field research center, to identify whether the woman was using contraception. As soon as she stopped contraception, if any, and attempted to conceive, she started recording daily diary on reproductive information such as menstrual bleeding and associated symptoms, as well as various exposures to occupational hazards. Daily samples of first-void morning urine were also collected. Subjects were instructed to store the samples in the refrigerator until they submit them to the field research center located in the plant. Diaries and the urine samples were submitted to the center twice a week. The diary recording and urine collection were terminated if the woman became clinically pregnant, dropped out of the study, or recorded the diary for one year.

Participation rate was greater than 95% among eligible women. Among those, a total of 357 women agreed to participate and were enrolled for the study during 1994-1998. This study was approved by the institutional review boards of Harvard School of Public Health and Beijing Medical University.

Identification of conception

Daily urine samples were analyzed for *human chrionic gonadotropin* (hCG) by *immunoradiometric assay* (IRMA) method developed by O'Connor et al. using a combination of anti-fragment B204 and anti-intact B109 clones. Normal nonconceptive levels of hCG was determined from the urine samples of 2608 days contributed by 46 sterilized Chinese women who did not have any medically diagnosed disease. The rise of hCG levels above control level was defined following the steps used by Wilcox (1988). Any two consecutive days in the samples from sterilized women did not rise above 0.6 ng/mL in our data. Three consecutive days above this level was defined to be a rise in the hCG level, indicating a conception (Figure 3). The number of menstrual cycles between the beginning of attempting to conceive and the conception was assessed by daily menstrual diary.

Assessment of exposures

Exposure assessment for petrochemical workers is challenging because there are many chemicals present in the work environment. A specialized method of assessment was developed to address the complex nature of exposures in a petrochemical industry. Details were described elsewhere (Hu, 1998). Briefly, a detailed job activity interview was conducted by an industrial hygienist to identify all the tasks of individual workers. For each task, information was obtained on

the area where the task was performed, time needed to perform the tasks, frequency of the tasks, possibility for contact with pollutants of interest, personal protection equipment used, and years of work in the job. In addition, location maps or flow charts of the process were acquired for each subject's work area. According to a sturctured form, the information from the job activity interview was summarized into two variables: exposure intensity, ranging from 0 to 3, and distance from the source, ranging from 1 to 3. The two variables were multiplied to result in the Job Activity Exposure Index (JAEI), ranging from 0 to 9. The JAEI was obtained for benzene. Exposure to other solvents, including styrene, toluene, and xylene as a group, was coded as a binary variable.

Potential confounders

In addition to information on reproductive history and menstrual patterns, detailed information was collected on various potential confounders. These included; age, body weight and height, date of marriage, current and past contraceptive use, past pregnancy, active and passive smoking, indoor coal combustion, cooking oil fumes, alcohol consumption, diet, use of herbal medicines, heavy lifting, body position during work, rotating shift-work, perceived work stress based on 4 point scale ranging 0-3, and physical activities outside the workplace.

Statistical Analysis

Time to conception was defined as the number of menstrual cycles from stopping contraception to the time of conception. Kaplan-Meier survival analysis method was applied to compare the cycle specific rate of conception among strata of exposure variables and covariates. Cox proportaional hazard analysis was used to estimate the relative risk (fecundability ratio) between exposed and nonexposed group, adjusting for covariates.

JAEI for benzene was dichotomized by the median value for high and low exposure groups. A total of 90 subjects did not have job activity assessment interview, therefore they were missing JAEI. We developed a prediction model for these missing JAEI utilizing the plant and workshop names and self-report of benzene exposure in the baseline questionnaire. All the analyses were repeated with JAEI as a continuous variable for the purpose of comparison.

Results

The characteristics of the study population was summarized in Table 6. In general most variables were comparable among the exposure groups. The group without job activity interview had higher frequency of college education and lower exposure to dust and noise, reflecting that some workers in administrative departments did not participate the interview. Table 7 and Figure 4 shows the rate of conception in each exposure group. High exposure group had a slower rate of conception compared to the other groups. The group without job activity interview was the fastest in the rate of conception.

Fecundability ratios from Cox regression are presented in Table 7. High exposure group shows a significant reduction in fecundability compared to nonexposed group. The ratio became smaller after adjusting for confounders.

Table 6. Characteristics of study population by exposure groups

	None	Low	High	Unmeasured
(N)	(68)	(80)	(41)	(90)
	Mean (SD)			
Age, years	25.8 (2.2)	25.1 (1.8)	25.4 (1.6)	25.3 (1.7)
Height, m	1.61 (0.05)	1.61 (0.05)	1.60 (0.04)	1.62 (0.05)
Weight, kg	54.9 (7.5)	54.3 (7.1)	55.5 (8.0)	54.7 (8.8)
BMI, kg/m^2	21.3 (2.8)	20.9 (2.5)	21.6 (3.1)	20.8 (3.1)
Years at current job	6.1 (2.8)	5.6 (2.5)	5.9 (2.4)	5.3 (2.3)
	N (%)			
Education				
Middle or lower	3 (4.4)	6 (7.5)	4 (9.8)	10 (11.1)
High	53 (77.9)	60 (75.0)	30 (73.2)	59 (65.6)
College or above	12 (17.6)	14 (17.5)	7 (17.1)	21 (23.3)
Passive smoking at work				
Yes	4 (5.9)	7 (8.8)	3 (7.5)	10 (11.1)
No	64 (94.1)	73 (91.2)	37 (92.5)	80 (88.9)
Passive smoking at home				
Yes	39 (63.9)	35 (53.8)	18 (48.6)	41 (60.3)
No	22 (36.1)	30 (46.2)	19 (51.4)	27 (39.7)
Dust exposure				
Yes	9 (13.2)	10 (12.5)	5 (12.2)	7 (7.8)
No	59 (86.8)	70 (87.5)	36 (87.8)	83 (92.2)
Noise exposure				
Yes	38 (55.9)	38 (47.5)	22 (53.7)	45 (50.0)
No	30 (44.1)	42 (52.5)	19 (46.3)	45 (50.0)
Tea Drinking				
Yes	21 (30.9)	31 (38.8)	19 (46.3)	33 (36.7)
No	47 (69.1)	49 (61.3)	22 (53.7)	57 (63.3)
Pill ever use for contraception				
Yes	2 (2.9)	4 (5.0)	2 (4.9)	3 (3.3)
No	66 (97.1)	76 (95.0)	39 (95.1)	87 (96.7)

Table 7. Unadjusted and adjusted* fecundability ratio (RR) and 95% confidence interval (CI) compared to nonexposed group (N=68)

	N	RR	95% CI	p value
Model I (unadjusted)				
Exposure unknown	90	1.25	(0.80, 1.97)	.33
Low exposure	80	0.91	(0.57, 1.44)	.67
High exposure	41	0.56	(0.30, 0.95)	.03
Model II (adjusted)				
Exposure unknown	90	1.17	(0.74, 1.86)	.50
Low exposure	80	0.84	(0.53, 1.35)	.46
High exposure	41	0.46	(0.24, 0.85)	.01
Model III (adjusted)				
Exposure unknown	90	1.12	(0.74, 1.69)	.59
Exposure Index	121	0.85	(0.74, 0.96)	.01
Model III (with PEI, adjusted)†				
Exposure unknown	33	1.20	(0.66, 2.16)	.55
Low exposure	114	0.91	(0.60, 1.40)	.68
High exposure	55	0.65	(0.38, 1.12)	.12
Model IV (with PEI, adjusted)†				
Exposure unkonwn	33	1.09	(0.63, 1.89)	.75
Exposure Index	169	0.88	(0.79, 0.99)	.03

*Covariates adjusted for: age, BMI, shiftwork, work stress, passive smoking, and tea drinking
†Nonexposed group, N=77.
PEI: Predicted Exposure Index

Figure 3. An example of hCG rise pattern

Figure 4. Comparison of conception rates by Kaplan-Meier curve

(figures attached at the end of the report)

VI. Organic solvent exposure and birth outcomes

Methods

Study population

We enrolled female employees in Yanshan Petrochemical Corporation, in Beijing, China (BYPC), who visited hospitals for delivery during 1994-1998. BYPC is a large petroleum and chemical processing plant made up of 17 different but well integrated production plants and institutes. As of 1998 the corporation employs approximately 39,000 production workers and approximately 40% are women. The Yanshan Workers' Hospital is a large hospital under a contract with BYPC to provide comprehensive health care for the employees. The obstetrics department of the hospital has 50 delivery beds and is exclusively designated for maternity care for the employees. Every female employee of the BYPC is entitled to receive the care including general health examination, pregnancy testing, regular antenatal follow-ups, and delivery service. For normal term delivery, each prospective mother is scheduled for 14 antenatal visits from the pregnancy diagnosis to delivery. All women who visited the obstetrics department of the hospital to deliver a baby was contacted for this study. Eligibility was restricted to the woman aged 20 - 40. Among eligible subjects, participation rate was over 98%. A structured interview questionnaire was administered to all participants, to collect information on reproductive history and various exposures and potential confounders.

Aessessment of birth outcomes

Gestational age of the fetus was determined by the last menstrual period identified at the clinical diagnosis of pregnancy. In the delivery unit, the staff nurse filled out a record of the delivery procedure and health status of the mother and infant, including birth weight. This record was combined with the baseline questionnaire. For live births, the outcomes of main interest was birth weight adjusting for gestational age.

Assessment of exposures

Upon enrollment, information was obtained by an interview questionnaire for each woman on the plant name, workshop name, job title, and a checklist of chemicals handled. A specialized method of assessment was developed to address the complex nature of exposures in a petrochemical industry. Details were described elsewhere (Hu, 1998). Briefly, detailed information of the work process in each workshop was obtained including location maps or flow charts of the process. Individual's information on plant, workshop, job title was evaluated in combination with work process information by a structured format. According to the evaluation, exposure status was classified into three categories: "No exposure to solvents", "Exposure to benzene", and "Exposure to other solvents". Exposure to other solvents indicates the possibility of exposure to any of styrene, toluene, and xylene, but not benzene.

Potential confounders

In addition to information on reproductive history and menstrual patterns, detailed information was collected on various potential confounders. These included; maternal age, body weight and height at or prior to the pregnancy, date of marriage, past contraceptive use, past pregnancy, active and passive smoking, indoor coal combustion, cooking oil fumes, alcohol consumption, diet, use of herbal medicines, body position during work, rotating shift-work. Degree of exertion, heavy lifting, noise, and perceived work stress were asked based on 4 point scale ranging 0-3.

Statistical Analysis

No subjects had more than one birth during the study period. The relationship between birth weight and gestational age was examined with smoothing plots using generalized additive modeling techniques. Mean birth weight adjusting for gestational age was compared between different exposure and covariate categories.
Multiple linear regression was used to estimate the effect of exposure variables adjusting for covariates. Maternal age, prepregnancy body weight and height were treated as linear terms in the models. Model selection was carried out by first examining the full model including all the variables of interest. Covariates that did not change the association between the exposure and outcome and were not significant independent predictors were excluded from the final model.

Results

Characteristics of the study population are shown in Table 8 by exposure group. Compared to nonexposed group, benzene exposed group had lower birth weight, lower education, more frequent shift work, higher noise, higher passive smoking at home, and more frequent dysmenorrhea. After adjusting for confounders, linear regression showed that benzene exposure group had 62g reduction in birth weight compared to nonexposed group. "Other exposure" group showed 58g reduction in birth weight (Table 9). To examine whether the covariates modify the association, stratified analyses were conducted for each of the covariates, adjusting for the rest of the covariates (Table 10). In both benzene exposure and other exposure groups, the reduction in birth weight was greater in the lowest educational category. The reduction was greater in women who had no previous pregnancy, compared to women with previous pregnancy history. Lowest age tertile and stress was associated with significantly reduced birth weight in benzene exposed group.

Table 8: Characteristics of the study population

	Non-exposure N=457	Other Solvents N=414	Benzene N=366
	Mean ± SD	Mean ± SD	Mean ± SD
Age, year	28.2 ± 2.5	28.2 ± 2.5	27.9 ± 2.0
Employee year, year	6.2 ± 2.9	6.6 ± 3.0	6.7 ± 2.5
Age of menarche, year	13.9 ± 1.5	13.9 ± 1.5	13.9 ± 1.3
Birth weight, g	3466 ± 432	3396 ± 430	3381 ± 452
Gestational age, week	40.0 ± 3	39.9 ± 2	39.8 ± 1.5
		Percent	
Education			
Primary	10.1	24.4	9.3
Middle school	49.0	50.0	69.7
High school	23.8	15.0	12.5
College and above	17.1	10.7	8.2
Shift Work	15.8	19.1	49.2
Stress	19.5	15.2	16.2
Noise	12.7	33.8	42.4
Dust	8.1	10.4	7.9
Passive smoke at work	22.6	28.3	22.4
Passive smoke at home	44.6	48.6	51.1
Parity	38.3	43.7	40.4
Dysmenorrhea	40.5	47.1	44.8
Female	49.2	47.1	49.1

Table 9: Univariate and multivariate analysis of birth weight

	Crude			Adjusted#		
	β	SE	P-value	β	SE	P-value
Benzene exposure	-84.7	31.2	0.006	-62.1	31.5	0.049
Other exposure	-70.0	30.2	0.020	-57.6	29.1	0.048

Multiple linear regression models adjusted by age, education (less than middle school, middle school high school and college &above), passive smoke, work shift, dust, noise, stress, infant gender, gestational age, parity and dysmenorrhea.

Tables 10. Stratified analysis of benzene exposure with birth weight

	Benzene exposure		Other exposure	
	β# (SE)	P-value	β# (SE)	P-value
Age(tertile)				
1	-135.4(57)	0.019*	-40(55)	0.464
2	-50.2(52)	0.342	-74(49.2)	0.131
3	-26.4(55)	0.634	-40.4(49.7)	0.417
Employee year(tertiles)				
1	-46.7(50)	0.353	-28.2(44.4)	0.527
2	-97.3(60)	0.109	-108.5(58)	0.063
3	-32.6(53)	0.541	-23.5(52.6)	0.655
Age of menarche(tertiles)				
1	-83.9(52)	0.107	-85.4(47)	0.070
2	-72.1(54)	0.185	9.1(52)	0.861
3	-6.1(60)	0.918	-74.9(54)	0.167
Education				
Primary School	-202.2(97)	0.039*	-209.4(75)	0.006*
Middle School	-20.1(41)	0.631	1.3(42)	0.975
High school	-137.7(88)	0.122	0.008(77)	1.000
College or over	-34.2(76)	0.655	-178(66)	0.008*
Shift Work				
Dayshift	-70.6(38)	0.065	-49.9(32)	0.123
Nightshift	-54.4(62)	0.383	-21(72)	0.764
Stress				
No	-23.1(34)	0.503	-39.5(32)	0.218
Yes	-297.7(75)	0.000**	-77.7(71)	0.281
Noise				
No	-51.2(36)	0.157	-58.2(32)	0.078
Yes	-95.3(70)	0.175	-45.2(69)	0.514
Dust				
No	-48.3(31)	0.131	-43.1(30)	0.153
Yes	-68.5(42)	0.235	-51.1(32)	0.198
Passive smoke at work				
No	-89.3(35)	0.012*	-50.1(33)	0.139
Yes	26.4(67)	0.694	-31.4(58)	0.594
Passive smoke at home				
No	-46.2(41)	0.271	-73.8(38)	0.053
Yes	-86.1(47)	0.071	-46.7(44)	0.297
Parity				
No	-95.2(40)	0.019*	-75.3(37)	0.043*
Yes	-23(50)	0.642	-36.4(47)	0.438
Dysmenorrhea				
No	-65.5(42)	0.124	-36.3(38)	0.352
Yes	-60.4(47)	0.206	-89.5(44)	0.044*
Infant gender				
Male	-33.1(43)	0.445	-2.4(39)	0.950
Female	-88.7(46)	0.053	-121.4(43)	0.005*

Multiple linear regression models with adjustment for age, education (less than middle school, middle school , high school and college or above), passive smoke, work shift, dust, noise, stress, infant gender, gestational age, parity and dysmenorrhea.
* P<0.05, ** P<0.001.

VII. Methological works on exposure assessment

Methods

In this study, 132 female petrochemical workers were quantitatively assessed exposure of benzene, toluene, styrene and xylene by personal air sampling. Two quantitative exposure indices were calculated: time-weighted average across the entire work shift, and average of the peak exposure during short duration tasks that involved solvent handling.

The validity of 132 female workers' self-assessment of their exposure to benzene, toluene, styrene and xylene were examined by compare it with actual measurements as well as with an assessment made by an occupational hygienist. Information on self-assessed exposure status was obtained by questionnaires administrated to the subjects. Full shift air samples were gathered at the same time. In addition, the exposure status was also assessed by an occupational hygienist's evaluation of the production processes in the subjects' work area. Several measures of validity were used including: sensitivity and specificity, Cohen's kappa, and overall proportion of agreement.

Critical time window is a period of time during which the exposure is etiologically related to the adverse health outcomes. It is speculated that the increased susceptibility of the host in the critical time window is caused by a lowing of the threshold level. Therefore, exposures above the threshold and inside the critical time are etiologically relevant. The critical time windows are especially important when the exposures are unevenly distributed because only exposures exceeding the threshold level and inside the critical time window will cause the adverse health consequences. However, cumulative exposure that ignores the critical time window is primarily used as the exposure index for epidemiolgic studies. Because evidence demonstrated that critical time windows exist in many reproductive processes and exposures profiles are likely to be unevenly distributed in petrochemical plants because of the accident-like events ("unscheduled events"), exposure measurement error caused by using cumulative exposure as an exposure index is expected. Computer simulation was used to investigate the effects of exposure measurement error on the estimation of odds ratios when there is a time window. Six hundred male workers exposure to benzene during 75-day spermatogenesis and their wives' early spontaneous abortion events were simulated. A hypothetical critical time window was assumed during the spermatogenesis.

Results

The workers' average exposures to benzene, toluene, styrene and xylene were 0.112 ppm, 0.041ppm, 0.032 ppm and 0.020 ppm respectively. The peak exposures for benzene, toluene, styrene and xylene for the tasks involving solvent handling averaged 1.22 ppm, 0.19ppm, 0.15 ppm and 0.06 respectively. The correlation coefficients of the full-shift exposure and peak exposure for benzene, toluene, styrene and xylene were 0.87, 0.73, 0.58 and 0.76 respectively. The maximum of the peak exposure to benzene, toluene, styrene and xylene was 74.3 ppm, 2.7 ppm, 2.0 ppm, and 0.7 ppm, respectively (Figures 5, 6).

There was a fair agreement between workers' self-report and measurement or professional assessment on benzene and styrene exposure, even though the open-ended questionnaire was used for self-assessment of exposures. The sensitivity, specificity, Cohen's kappa and overall proportion of agreement for benzene and styrene were (0.70, 0.62, 0.28, 0.68) and (0.39, 0.94, 0.38, 0.85) respectively (Tables 11, 12). Poor agreement was found on toluene and xylene when open-ended question was asked. However, when the exposure status on xylene were asked in the checklist form, the sensitivity, specificity, Cohen's kappa and overall proportion of agreement of self-assessed exposure status on xylene increased to 0.37, 0.81, 0.27 and 0.62 respectively. The disagreement was caused mainly by underreport of the exposures by the subjects. Similar results were reached when self-

assessment was compared with professional assessment. Fair agreement was found between professional assessment and measurement on benzene, styrene and xylene exposures. The sensitivity, specificity, Cohen's kappa and overall proportion of agreement for the benzene, styrene and xylene were (0.47, 0.76, 0.17, 0.55), (0.60, 0.95, 0.60, 0.89) and (0.57, 0.64, 0.21, 0.61) respectively (Table 13). There was poor agreement between professional assessment and measurement on toluene. From this study we conclude that self-assessment, when questionnaires were used properly, can provide useful information on subejcets' exposure status. The performance of self-assessment can be as good as professional assessment.

In the simulation experiment, the results demonstrate that when there is a critical time window, the use of cumulative dose can obscure a hypothetical "true" odds ratio of 3 to 1. The factors influence the odds ratio the most were the size of the critical time windows (Figure 7), the threshold of the exposure (Figure 8), and the geometric means of the accident-like peak exposure events ("unscheduled events") (Figure 9).. The frequency of unscheduled events had only slight effects on the odds ratio, while high frequency events tending to attenuate the true odds ratio slightly more.

Table 11. Agreement between self assessed exposure status and measurement on benzene, toluene, styrene and xylene

	Overall Proportion Agreement	Sensitivity	Specificity	Cohen's Kappa
Benzene	0.68	0.70	0.62	0.28
Toluene	0.06	0.024	0.83	-0.01
Styrene	0.85	0.39	0.94	0.38
Xylene	0.62	0.37	0.81	0.20

Table 12. Agreement between self assessed exposure status and professional assessed exposure on benzene, toluene, styrene and xylene

	Overall Proportion Agreement	Sensitivity	Specificity	Cohen's Kappa
Benzene	0.58	0.75	0.47	0.20
Toluene	0.68	0.025	0.97	-0.10
Styrene	0.91	0.58	0.96	0.60
Xylene	0.67	0.40	0.78	0.19

Table 13. Agreement between professional assessed exposure status and measurement on benzene, toluene, styrene and xylene

	Overall Proportion Agreement	Sensitivity	Specificity	Cohen's Kappa
Benzene	0.68	0.70	0.62	0.17
Toluene	0.06	0.024	0.83	-0.005
Styrene	0.85	0.39	0.94	0.60
Xylene	0.62	0.37	0.81	0.21

Figure 5-9. See attached figures.

Conclusions

Strengths of the study

1. A field study exploiting a recently developed highly sensitive and specific biochemical assay for the hCG has confirmed earlier suggestions in the literature that more pregnancies are lost before being recognized by women than after they are clinically recognized (Wilcox et al. 1988). A prospective study using the recent, improved, more specific assays, aimed at examining the risk of infertility and early pregnancy loss due to occupational or environmental exposures, would provide sensitive, accurate and unbiased estimates of the effects of exposure. This is one of the largest occupational epidemiologic studies to use the highly sensitive and specific hCG biomarker to determine conception and fetal loss.

2. Most previous studies are retrospective in nature, and the estimation of occupational exposure was usually based on type of industry or occupation rather than by specific agents and exposure category. The importance of this distinction has been demonstrated by a study showing that an association of central nervous system malformations with exposure to solvents, which had already been demonstrated, was not found when occupational titles were used as a proxy for exposure. The prospective design obviates the potential biases in retrospective study, such as difficulties of detecting early losses, uncertainty about temporal relations, selection bias, recall bias, reporting bias, etc. In addition, the prospective design allows accurate characterization of exposure status and it is possible to study multiple outcomes related to specific exposures. A common problem for prospective study is the low yield (inefficiency) of such an approach, and a costly and lengthy period of follow up required. China offers particular advantages in this regard because nearly all couples who plan a pregnancy identify themselves for offical permission. In China, the number of births in each community is planned and assigned by the local family planning administration. Any woman who wants to have a child must first register and obtain permission from the local family planning administration. Prenatal care and delivery service are provided at designated hospitals. Our studies utilized the characteristics of Chinese health care system to identify and enroll study participants for both retrospective and prospective components of the study.

3. More than 90% of all reproductive age women in urban areas in China work outside the home. A large proportion of pregnant women continue to work until close to delivery. This minimizes the possibility of "unhealthy worker effect", which may occur if fertile women tend to leave work while infertile women stay at work.

4. Prospective studies which only include planned pregnancies could introduce selection bias if the exposed and unexposed have a different probability of being excluded because of not planning conception. However, in this study, we selected a cohort of married women who were expected to become pregnant. It is their personal desire to have a child, and the birth permission from family planning administration expires after a specific period of time. These pregnancies are not likely to be interrupted or confounded by induced abortions (except for medical reasons). The majority of the births to these women are expected to be first order due to current one child family policy. Thus parity is not an important confounder in this study. These sample characteristics minimize the selection bias introduced by studying only planned pregnancies if the exposed and unexposed have different probabilities of being excluded because of not planning. In addition, the age range for these women is relatively narrow (mostly 20 to 35 yrs.).

5. This study included detailed exposure assessment for exposure agents and levels. Exposure information was obtained through occupational records, questionnaire, and individual time-activity data. Validation study was conducted with measurements of personal air samples.

6. Participation and compliance have been excellent throughout the study, and we were able to obtain detailed information on a variety of environmental and occupational agents as well as personal confounding factors.

7. In addition, this study was conducted in collaboration between Harvard Occupational Health Program and Beijing Medical University, a medical school with an academic leadership in China. This project has developed an excellent paradigm and a well functioning infrastructure for international collaboration in environmental and occupational epidemiology research.

8. In conclusion, our studies show that low level exposures to benzene and other organic solvents are associated with various adverse reproductive outcomes. Our study applied improved methods for the assessment of reproductive outcomes and petrochemical exposures.

Public Health Implications

From 1970 to 1990, the proportion of women in the civilian labor force increased from 43% to 58%. Two-thirds of women of childbearing age are employed outside the home. Many of these women have entered occupations traditionally held by men, which may involve potential exposures to reproductive hazards. Although the reproductive system might be more sensitive to the adverse effects of low-level exposures, regulatory standards are often based on acute health effects or cancer risk. Data on reproductive hazards are usually ignored in decision-making. It has become increasingly important to consider non-cancer outcomes in risk assessment. Reproductive risk of benzene has not been well studied previously, mainly due to the challenges in study design, although there have been suggestive evidence to support further investigation. Compared to cancers for which induction times are long, reproductive outcomes, such as endocrine disturbance and early fetal loss, reflect the risk of relatively shorter exposures. Moreover, evaluation of risk from short-term high exposure is especially important for organic solvents because their exposure pattern is typically highly variable. Exposure to benzene is common in both the general population and in the workplace. Although the level of exposure in most modern industrial working environments is controlled below the limit regulated by OSHA, our results show that even low-level occupational exposure to benzene and other solvents is linked to a broad spectrum of adverse reproductive outcomes, including menstrual disorders, decreased fecundability, spontaneous abortion, and low birth weight. A coherent trend was obtained from both retrospective and prospective studies.

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Figure 1. Reproductive Health Research Field Operations

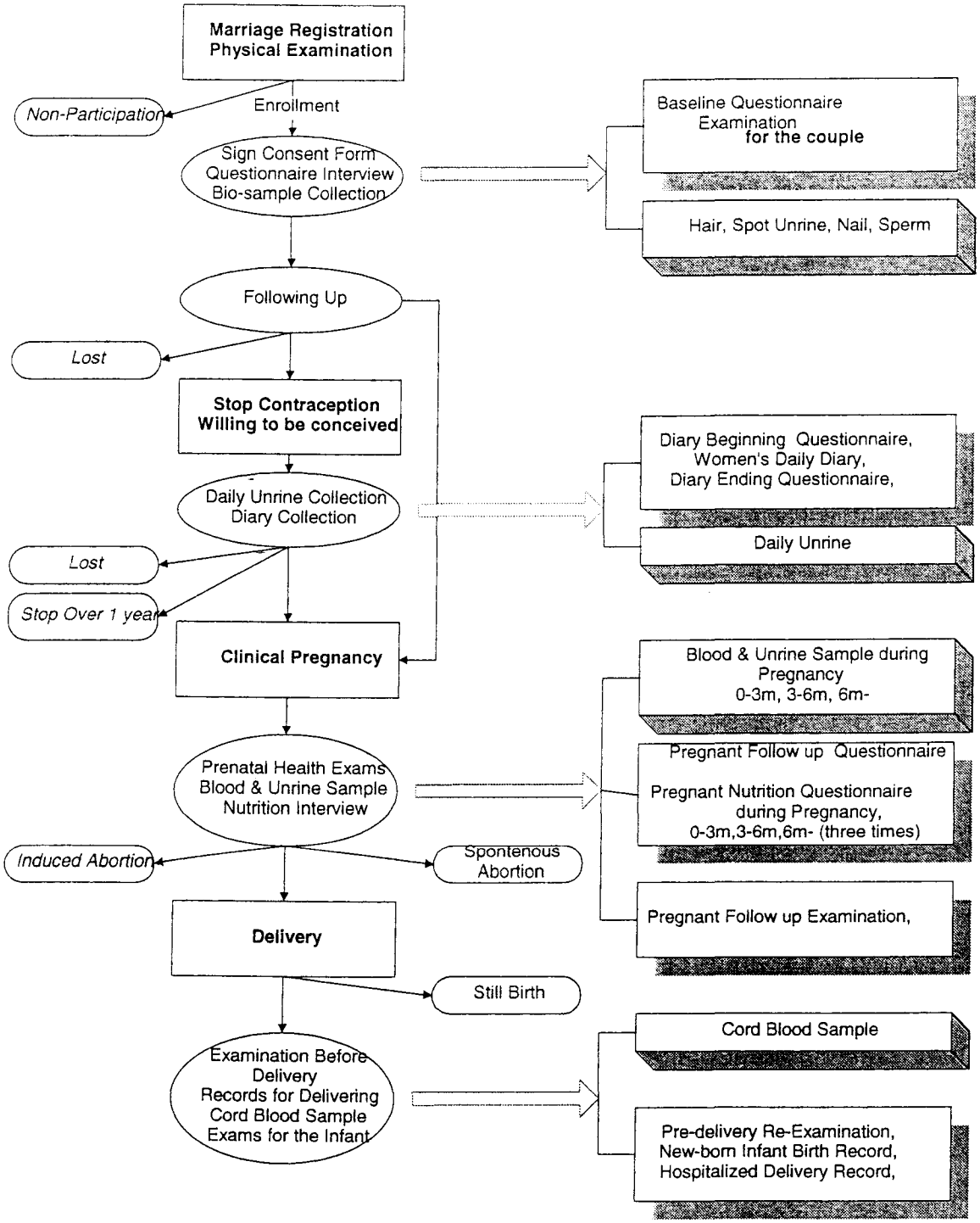
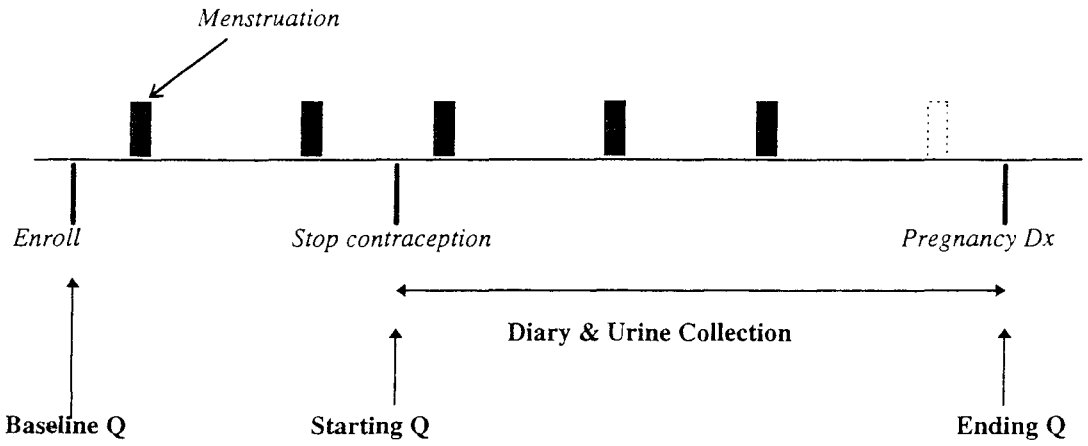


Figure 2. Time course diagram for the follow-up of a study participant



Reasons for ending daily follow-up:

1) Clinical pregnancy diagnosis
2) One year follow-up without clinical pregnancy
3) Drop-out

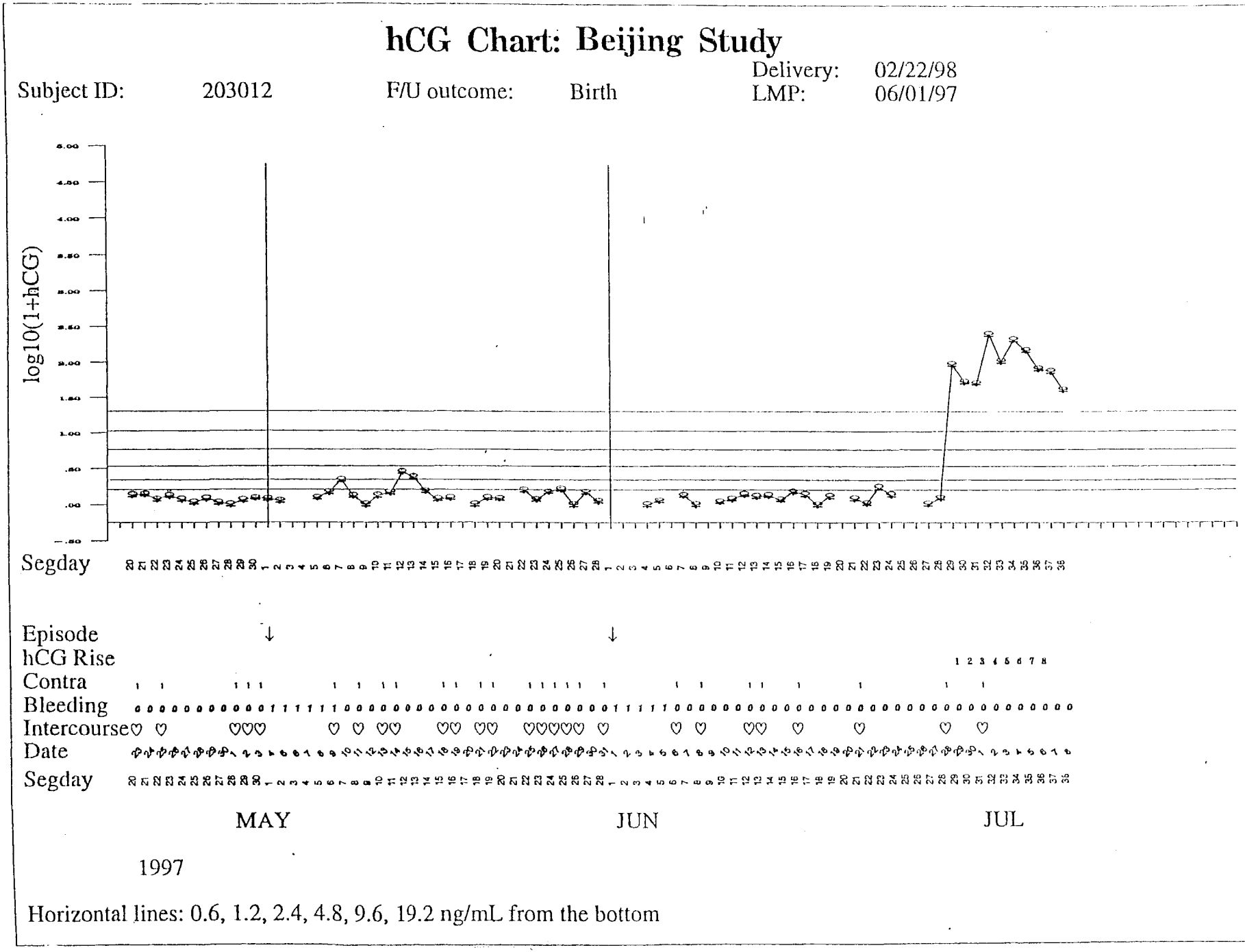


Figure 3. An example of hCG rise pattern

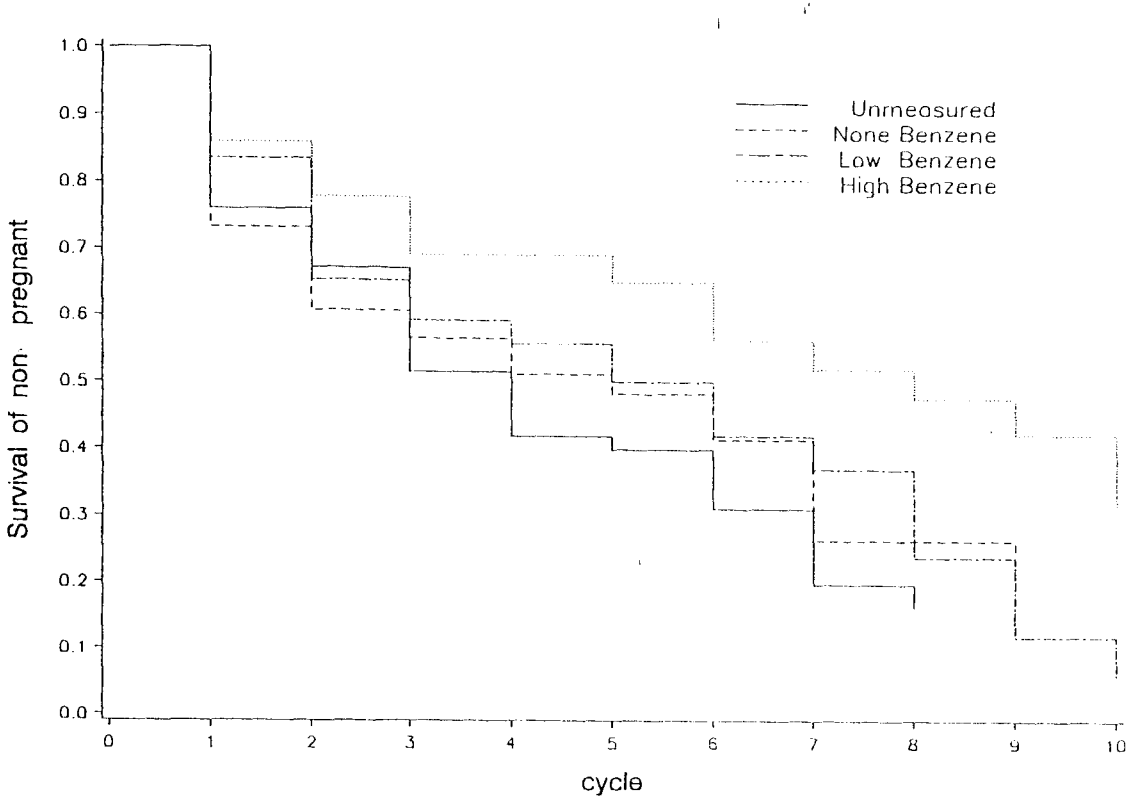
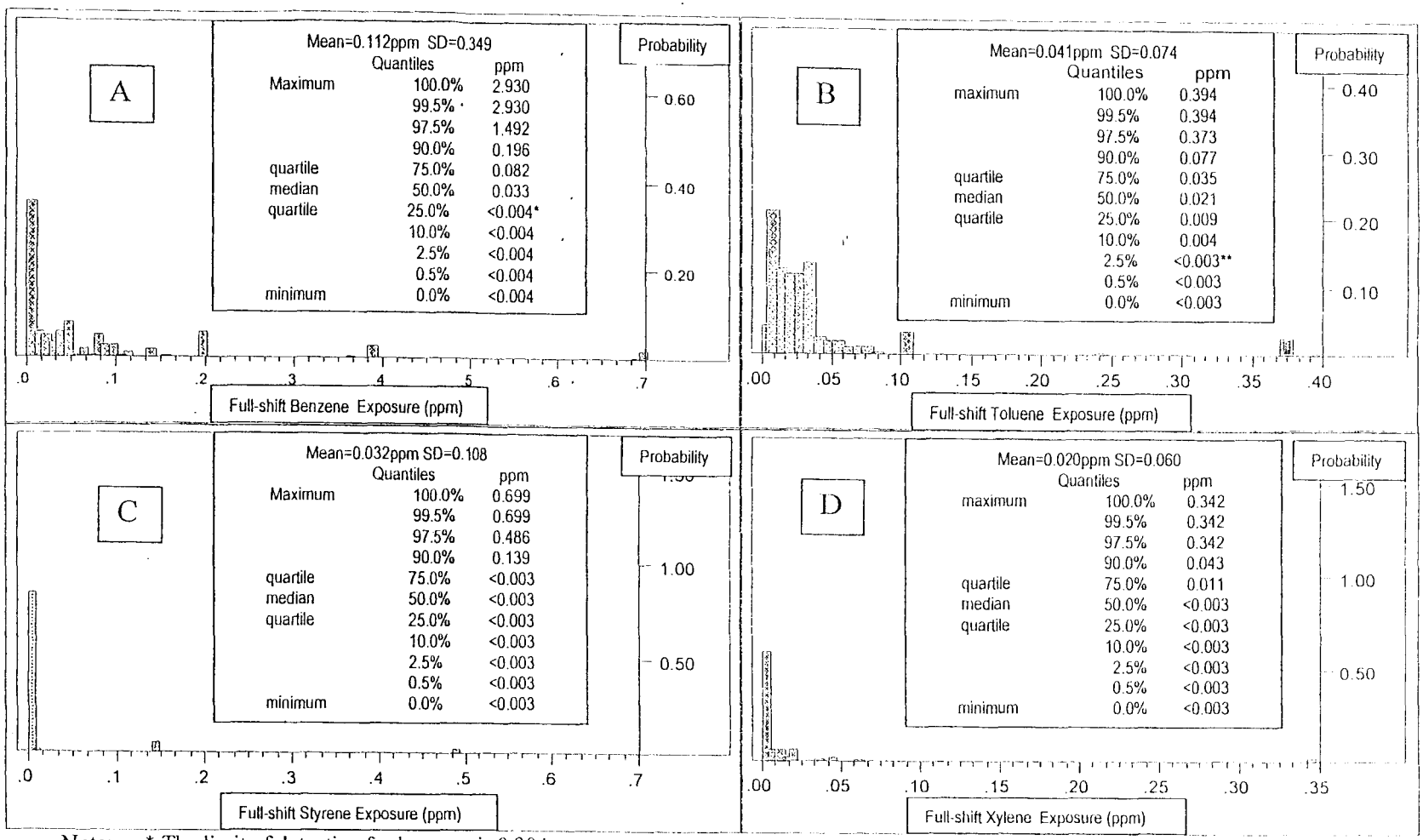
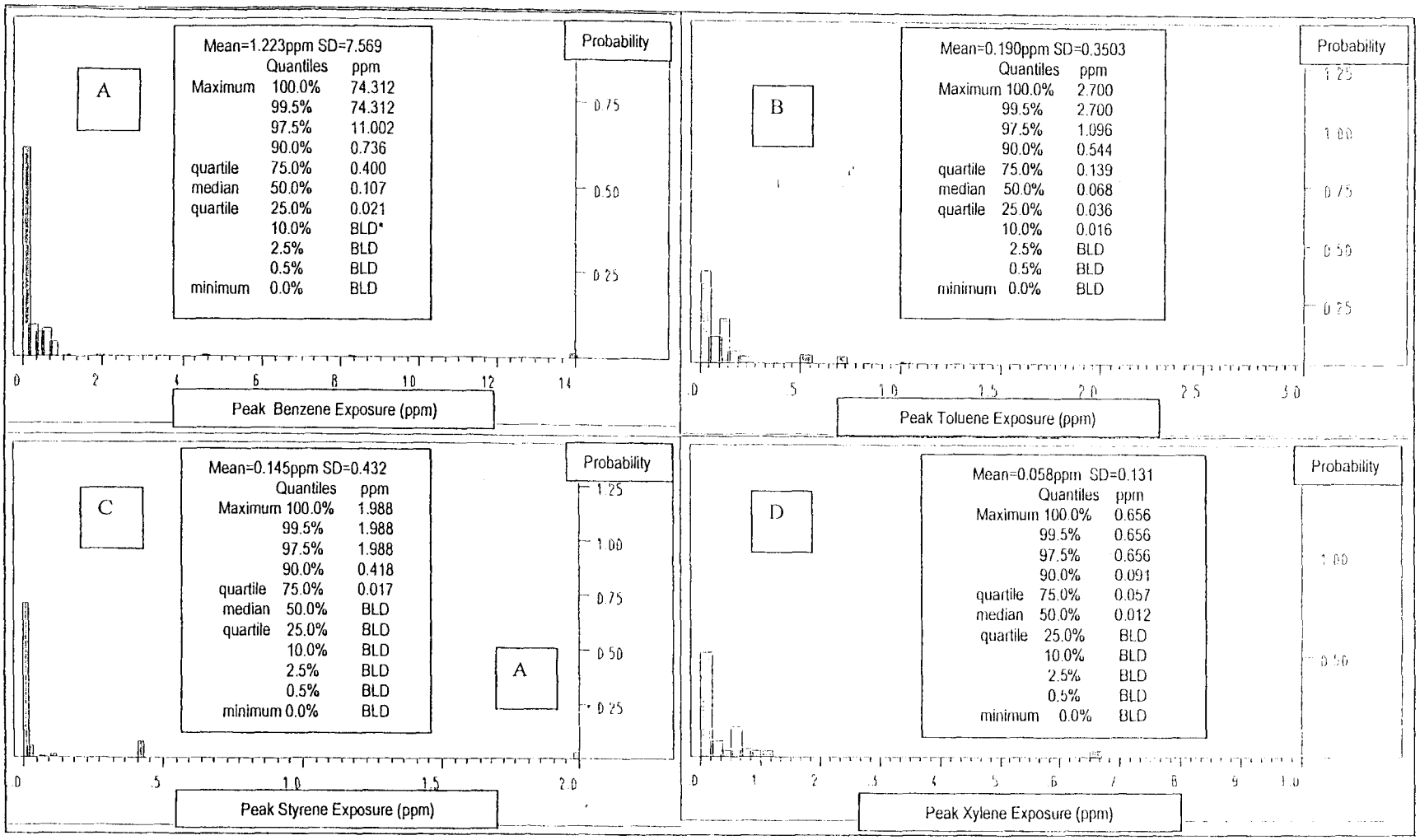


Figure 4. Comparison of conception rates by Kaplan-Meier curve



Note: * The limit of detection for benzene is 0.004ppm.
** The limit of detection for toluene, styrene and xylene is 0.003ppm.

Figure 5. A). Distributions of full-shift benzene exposures. B). Distributions of full-shift toluene exposures. C). Distributions of full-shift styrene exposures. D). Distributions of full-shift xylene exposures.



Note: * The limit of detection for benzene is 0.004ppm. The limit of detection for toluene, styrene and xylene is 0.003ppm.

Figure 6. A). Distributions of peak benzene exposures. B). Distributions of peak toluene exposures. C). Distributions of peak styrene exposures. D). Distributions of peak xylene exposures.

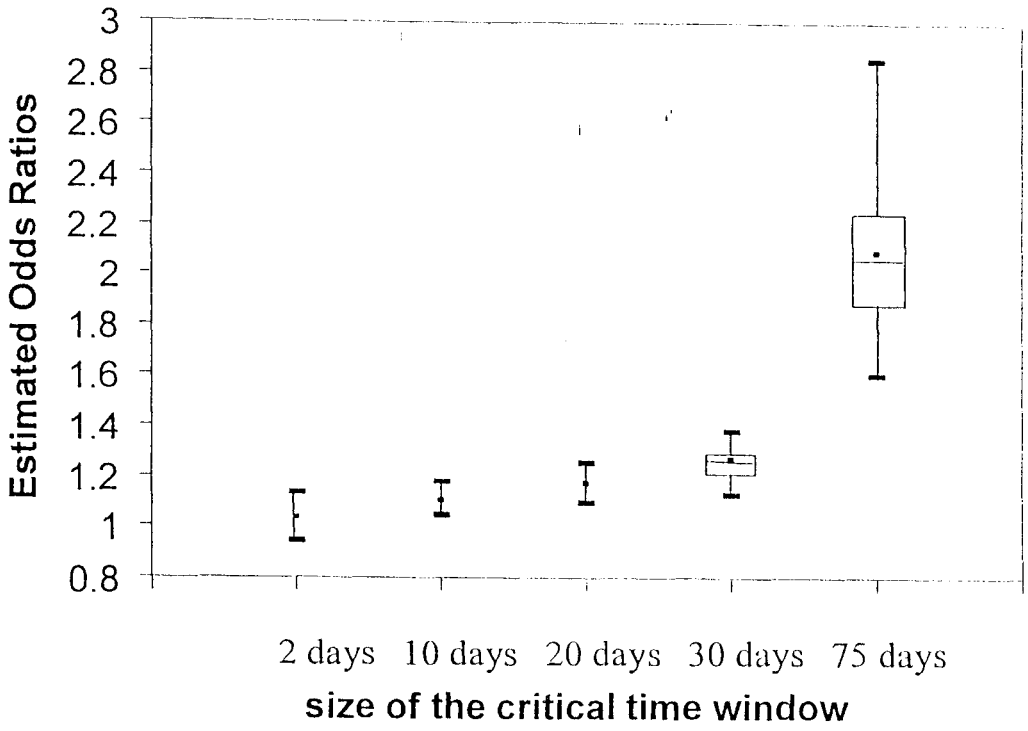


Figure 7. The effect of the size of the critical time window on the estimated odds ratio (the true odds ratio is 3)

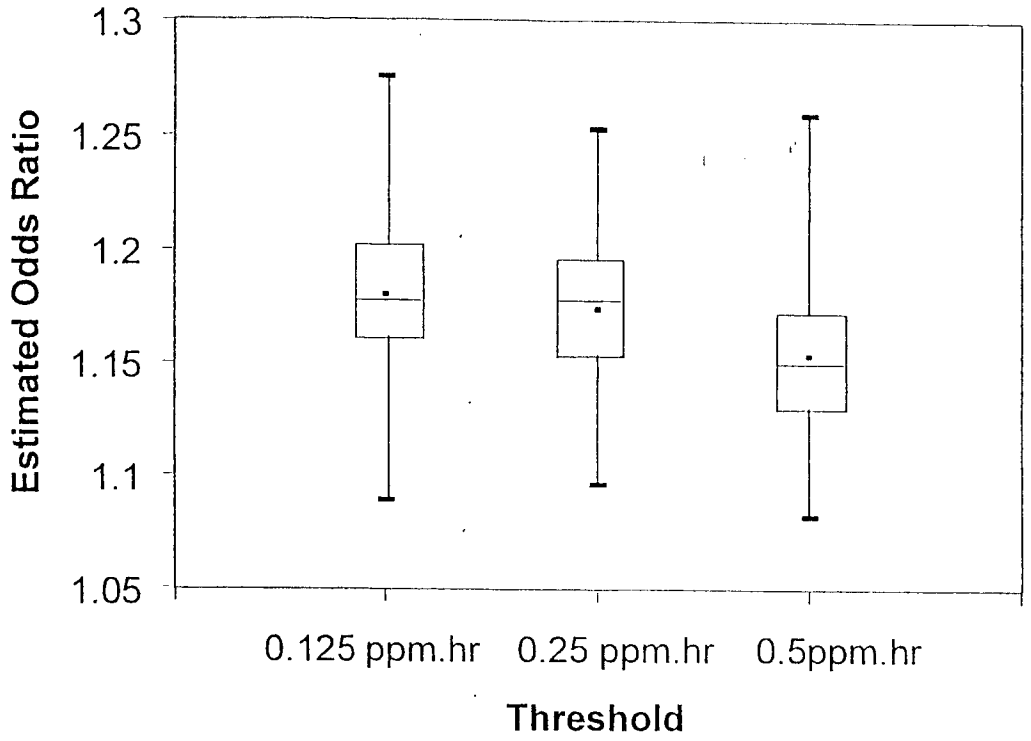


Figure 8.. The effect of the assumed threshold of exposure on the estimated odds ratios

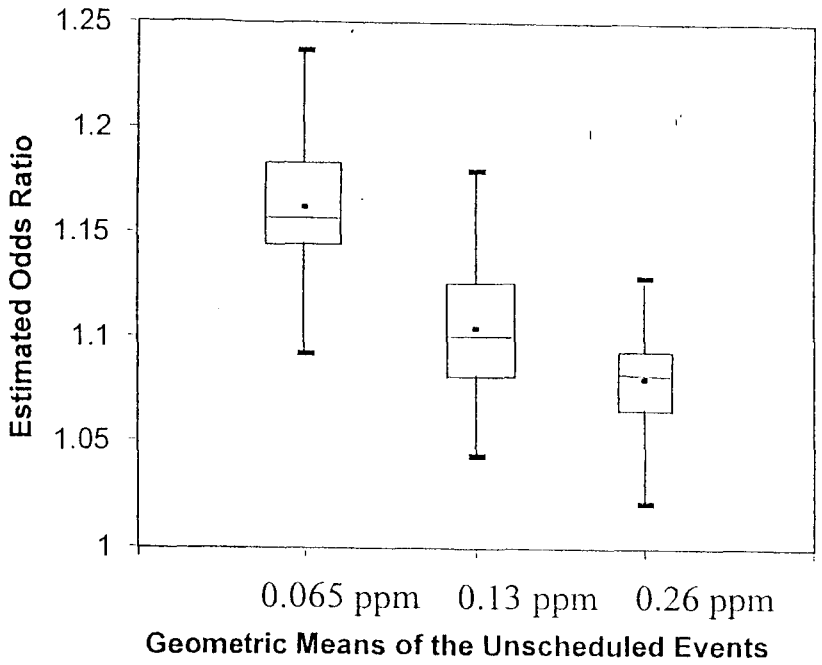


Figure 9.. The effect of the geometric means of the unscheduled events on the observed odds ratios

Publications

Xu X, Cho S-I, Sammel M, You L, Cui S, Huang Y, Ma G, Padungtod C, Pothier L, Niu T, Christiani D, Smith T, Ryan L, Wang L. Association of petrochemical exposure with spontaneous abortion. Occupational and Environmental Medicine 1998:55:31-36.

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Planned Publications

Thurston SW, Ryan L, Christiani DC, Snow R, Carlson J, You L, Cui S, Ma G, Wang L, Huang Y, Xu X. Petrochemical exposure, ergonomic factors and menstrual disturbances. (Submitted)

Cho S-I, Ryan L, Sammel MD, Christiani DC, Xu X. Sequential imputation of missing data in daily menstrual diary. (Submitted)

Hu Y, Smith TJ, Xu X, Wang L, Chen D, Li G, Watanabe H, Kono K, Orita Y, Dong H, Pan X, Christiani DC. Exposure assessment for reproductive chemical hazards for female petrochemical workers. (In preparation)

Hu Y, Smith TJ, Xu X, Wang L, Chen D, Li G, Watanabe H, Kono K, Orita Y, Dong H, Pan X, Christiani DC. Comparison of self-assessed solvent exposure with measurement results and occupational hygienist assessed exposure. (In preparation)

Hu Y, Smith TJ, Ryan L, Christiani DC. Exposure misclassification due to critical time windows in reproductive epidemiology studies. (In preparation)

Cho S-I, Damokosh A, Hu Y, Chen C, Ryan L, Smith T, Christiani DC, Xu X. Effects of exposure to organic solvents on menstrual cycle length. (In preparation)

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Appendix I-1:

Exposure Assessment Questionnaire

Sampling ID _____ Project ID _____
Sampling Date ____/___/____. Subject Name _____
Sampling Time

Time Pump on _____ Time Pump off _____ Duration _____ (minute)
Rate_____(cc/minute) Volume _____(cc)

Weather _____ Temperature _____
Humidity _____ Wind Direction/velocity _____

Working Diary_I

Questionnaire ID _____
Data of Interview ___/___/___ Interviewee_____
Plant _____
Workshop_____
Production Line_____
Job Title_____
JobDescription_____
_____

Detailed Description for Each Task

Task1:
Task Description _____

_____

Location _____

_____

Time Need For This Task: _____ Minute
Daily Frequency For This Task: _____
Skin Contact With Chemicals: _____(Yes, No)
Use of Personal Protection Equipment: _____

_____

Working Diary__II

Questionnaire ID_____
Data of Interview ___/___/___ Interviewee_____

Task Number: ____
Task Discription _____

_____

Location _____

_____

Time Need For This Task: _____ Minute
Daily Frequency For This Task: _____
Skin Contact With Chemicals: _____(Yes, No)
Use of Personal Protection Equipment: _____

_____

Task Number: ____
Task Description _____

_____

Location _____

_____

Time Need For This Task: _____ Minute
Daily Frequency For This Task: _____
Skin Contact With Chemicals: _____(Yes, No)
Use of Personal Protection Equipment: _____

_____

Reproductive hazards of self assessed exposure status.

Hazards	Mild	Medium	High
Benzene			
Toluene			
Styrene			
Xylene			
Carbon disulfide			
Carbon tetrachloride			
Dichloromethane			
Epichlorohydrin			
Ethlene glyco monoethl ether			
Formamides			
Xylene			
Acrylonitrile			
Benzo-a-pyrene			
Carbon monoxide			
Cyanides			
Di-n-butylphthalate			
Dinitrotoluene			
Clycidyl eithers			
Methyl chloride			
Polychlorinated biphenyl			
Vinyl chloride			
Arsenic			
Boron anhydride			
Cadmium			
Chromium			
Copper			
Lead			
Manganese			
Mercury			
Nickel			
Selenium			
Acrolein			
Aldrin			
Chlordecone			
Cyanazine			
DDT			
Diedrin			
Dinoseb			
Endrin			
Methyl parathion			
1,2-dibromo-3-chloropropane			
Ethylene dibromide			
Ethylene oxide			
Ethylene thiourea			
Haxachlorobenzene			
Thiram			

Picloram
Toxapene
Trichlorophenoxyacetic acide
Warfarin
Benomyl
Non ionizing radiation
Video display terminal
Physical exertion
Noise
Vibration

Appendix I-2:

ID_____

REPRODUCTIVE HEALTH BASELINE QUESTIONNAIRE
(For Wife and Husband)

IDENTIFICATION

Subjects' Names: Wife's _____ Husband's _____

Social Security ID: Wife's __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

Husband's __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

SURVEY PROCESS

Times of Visit	Date of Visit	Result of Visit			Interviewer's Name
		Refused	Absence	Finished	
First visit					
Second visit					
Third visit					

RESULTS - FORM REVIEW

Times of Form Review	Date of Form Review	Quality Comments			Examiner's Name
		Passed	Revised	Invalid	
First time					
Second time					
Third time					

Signature of Form Re-examiner:_____

I. GENERAL INFORMATION

1.1 Date of birth Wife __/__/__(M/D/Y), Husband __/__/__ (M/D/Y)
1.2 Place of birth _____
1.3 Ethnicity: 1. Han 2. Hui 3. Other Wife ___ Husband ___

1.4 Parents' Home Address:
Wife's _____ St./Av./Rd. #___Bd./Apt. #___Rm., _____ District, _____City,

_____ Province. Zip Code _ _ _ _ _ _. Tel (_ _ _)-_ _ _-_ _ _ _

Husband's _____ St./Av./Rd. #___Bd./Apt. #___Rm., _____ District, _____City,

_____ Province. Zip Code _ _ _ _ _ _. Tel (_ _ _)-_ _ _-_ _ _ _

1.5Current Address_____

1.5.1 How many years have you been at this current address? Wife ___ Husband ___
From _____ To _____
1.6 Previous Address_____

1.6.1 How many years have you been at this previous address? Wife ___ Husband ___
From _____ To _____
1.7.1 Education Wife ___ Husband ___
1) primary school & below 2) middle school 3) high school/secondary professional school
4) high professional school 5) college & above
1.7.2 Job Training
Place_____
From _____To_____
Major_____
1.8 How old were you at the time of marriage (years-old)? Wife ___ Husband ___

1.9 When did you get your Marriage Certificate? __/__/__ (M/D/Y)

1.10 When did live together after your wedding ceremony? __/__/__ (M/D/Y)

1.11 When did (do) you plan to have your first baby? Wife ___ Husband ___
1) right after getting married 2) in 1 year 3) in 2 years 4) after 2 years or more

II. GENERAL HEALTH STATUS

2.1 Did your have any of the following diseases? Yes___ No___
(if yes, please fill in below)

Order	Name of Disease	Dis.# Date(M/Y)	Diagnosis Hospital	Age of Onset,	Result Cure of Dis.	Main Drugs	Notes
For Wife							
1)							
2)							
3)							
4)							
For Husband							
1)							
2)							

3)
4)

Note: a. # of Diseases

01 varicella & herpes zonstic
02 nettle rash
03 tuberculosis
04 parotitis
05 asthma
06 bronchitis
07 pneumonia
08 flu
09 other respiratory diseases
10 hypertension
11 coronary heart disease
12 immune system disease
13 congenital heart disease
14 myocardium diseases
15 other heart diseases
16 hepatitis
17 stomach & duodenal ulcer
18 cholecystitis
19 nephritis
20 pyelonephritis
21 diabetes
22 hyperthyroidism
23 hypothyroidism
24 anemia
25 other blood diseases
26 hereditary diseases
27 Bobor's bacillus disease
28 other insect-transferred diseases
29 malignant tumors
30 cervical polyp
31 perineum tumor
32 vaginitis
33 cervicitis
34 myoma of uterus
35 sleep disorders
36 carcinoma of cervix
37 prolapse of uterus
38 irregular menstruation
39 carcinoma of uterus body
40 tumors of ovary
41 pelvic inflammatory disease
42 tumor of breast
43 others

b. Hospital of Diagnosis

1. hospital directly administrated by central government, municipal government and all ministries of the government
2. hospital at regional or provincial level
3. hospital at district or county level
4. hospital for primary care and hospital at township level
5. primary care post or private clinic

c. Outcome of disease

1. cured 2.improved 3.no change 4.degenerated

2.2 Have you been suffering from any of the above diseases which were diagnosed by your doctor?

Wife: Yes___ No___ Disease #___, #___, #___, other_____
husband: Yes___ No___ Disease #___, #___, #___, other_____

2.3 If yes, do you take medicine currently? (p0lease see drug # appendix)

Wife: Yes___ No___ Drug #___, #___, #___, other_____
husband: Yes___ No___ Drug #___, #___, #___, other_____

2.4.1 Have you ever been allergic to any sort of food? Wife___ Husband___
1. never 2. yes 3.not clear

2.4.2 Have you ever been allergic to any sort of drug? Wife___ Husband___
1. never 2. yes 3.not clear

2.4.3 Have you ever been allergic to any sort of pollen? Wife___ Husband___
1. never 2. yes 3.not clear

2.4.4 Have you ever been allergic to any sort of other material? Wife___ Husband___
1. never 2. yes 3.not clear

2.5 When did you take your latest X-ray examination?
Wife: __/__/__(M/D/Y) Husband: __/__/__(M/D/Y)
2.6 Could you tell me your weight and height?
Wife: height_____ (cm) Husband: height_____ (cm)
weight_____ (kg) weight_____ (kg)
weight at birth_____(kg) weight at birth_____(kg)
2.7 Have you ever been hospitalized? Wife___ Husband___
1.never 2.yes
If yes, 2.7.1 How many times have you been hospitalized? Wife____ Husband____
2.7.2 When was your last time in the hospital?
Wife: __/__/__(M/D/Y) Husband: __/__/__(M/D/Y)
2.7.3 What is the reason? Wife:_____
Husband:_____
2.8 Have you ever suffered from sleep disorders?
1. never2.yes
If yes, 2.8.1 What type?_____
2.8.2 How many times a week did this effect you?_____
2.9 Do you currently suffer from sleep disorders?
1.never 2. yes
If yes, 2.9.1 What type?_____
2.9.2 How many times a week does this effect you?_____
2.10 How long does it take you to fall asleep? _____

III. Occupation

1. Workplace - Current Previous
1.1 Place of work _____
Specific Area of Work _____
Job title_____
Job salary range_____

1.2 When did you begin this job? ___/___ (M/Y)

1.3 When did you end your last job? ___/___ (M/Y)

1.4 How long have you had this job? _____yrs

1.5 How many hours a week do you work at your present job? ____hours

1.6 Do you come into contact with any kind of toxic substances? Y/N
(if no, go to 1.7)
1.6.1 Name of the major toxic substance in daily work (please use code) wife:_____ husband: _____
_____ _____
_____ _____

1.6.2 Hours of daily contact with toxic substance wife:_____ husband: _____
1.6.3 Are there any protective measures taken? wife:_____ husband: _____
1. no 2. gauze mouth mask 3. gloves 4. gas mask
5. gloves+gauze mouth mask 6. gloves+gas mask 7. others
1.6.4 The concentration of the toxic substances is wife:_____ husband:_____
1. low 2. medium 3. high

1.7 Do you come into contact with dust in your daily work? Y/N
(if no, go to 1.8)
1.7.1 Name of the major dust (please use code) wife:_____ husband:_____
1.7.2 Hours of daily contact with dust wife:_____ husband:_____

1.7.3 Concentration of the dust that you contact is: wife:_____ husband:_____
1. low 2. medium 3. high
1.7.4 Are there any protective measures taken? wife:_____ husband:_____
1.not any 2.gauze mouth mask 3.dust mouth mask or mask set 4. others
1.8 Are you exposed to noise in your daily work? Y/N
(if no, go to 1.9)
1.8.1 Hours of daily exposure to noise wife:_____ husband:_____
1.8.2 Degree of noise in you work wife:_____ husband:_____
1. light 2. medium 3. heavy
1.8.3 Are there any measures for the noise protection taken? Wife: Y/N

1.9 Are you exposed to vibration in your daily work? Y/N
(if no, go to 2)
1.8.1 Vibration effects wife:_____ husband:_____
1. whole body 2. local part(s) of body
1.8.2 Hours of daily exposure to vibration wife:_____ husband:_____
1.8.2 Degree of the vibration in your work wife:_____ husband:_____
1. light 2. medium 3. heavy

2. What is the major position you use in your daily work? wife:_____
1. sitting 2. standing (on the same place) 3. bending 4. squatting
or kneeling 5. mobile 6.others
2.1 How many hours do you remain in these positions? (only ask female)
position 1._____ position 2._____ position 3._____
position 4._____ position 5._____ position 6._____

3. How often do you need to lift or move heavy goods in your job?
wife:_____ husband:_____
1. never 2. sometimes 3. always

4. What is the level of physical exertion in your job? wife:_____ husband:_____
1. light 2. medium 3. heavy

5. What is your work shift? wife:_____ husband:_____
1. day shift 2.night shift 3. 2-shift 4. 3-shift
5. 4-shift
6. The temperature in your workplace often is wife:_____husband:_____
1. normal room temperature 2. high temperature
3. low temperature 4. Outside temperature

7. The humidity in your workplace often is wife:_____husband:_____
1. normal room humidity 2. dry 3. moist

8. Is there any air conditioning at your workplace? Y/N wife:_____husband:_____

9. How stressed do you feel at your workplace? wife:_____husband:_____
1. not very 2. a little 3. very

10.Do your colleagues in your office or work room smoke Y/N wife:_____husband:_____
while they are on duty? (if no, go to 11)
10.1 How many smokers are in your office/work room? wife:_____husband:_____
10.2 About how many cigarettes do they smoke every day? wife:_____ husband:_____

11. Do you work in an office? Y/N wife: _____husband:_____
11.1. IF YES: How large is your office? (square meters) wife:_____husband:_____

12. How is your workplace heated? wife:_____husband:_____
1. central heating system 2. coal stove 3. others
(if answer 1 or 3 item, go to IV.)
12.1 Is there a chimney with your coal stove? Y/N wife:_____husband:_____
12.2 How much coal is burned each year? (Kg) wife:_____husband:_____

IV. Daily Physical Activities

1. What kind of transportation do you take to your work place? wife:_____husband:_____
1. walking 2. bicycle 3. bus or shuttle 4. car 5. others

2. How far is from your home from your work place? wife:_____husband:_____
1. <500m 2. 500m- 3. 1Km- 4. 5Km- 5. 10Km & over

3. How do you consider the stress level of your work? wife:_____husband:_____
1. not stressful 2. average 3. very stressful

4. How many hours do you spend doing housework? wife:_____husband:_____

5. How often do you play sports? wife:_____husband:_____
1. more than once a day 2. 4-6 times a week 3. 1-3 times a week
4. 1-4 times a month 5. less than once a month

5.1 What is the level of physical exertion during exercise? wife:_____ husband:_____
1. light (daily activities)
2. medium (heart beating after the activities)
3. serious (sweating after the activities)

V. Smoking Status

1. Do you smoke?
1) yes 2) no wife:_____ husband:_____
If no, ask question 2; If yes, continue.
1.1 At what age did you start to smoke: wife:_____ husband:_____
1.2 How many cigarettes do you smoke every day? wife:_____ husband:_____
1.3 Generally, how far do you draw smoke to your body?
1) into the mouth 2) into the throat 3) into the lungs wife:_____ husband:_____
1.4 Have you reduced the amount of smoking within the last year?
wife:_____ husband:_____
1.4.1 Why did you reduce the amount of smoking?
1) disease, disease name (code) wife:_____ husband:_____
2) (1) economic reason (2) objection from family members
(3) recognition the hazardous effects of smoking (4) other
wife:_____ husband:_____

2. Have you ever smoked?(one cigarette every day and continue half year or above
10 packages in total) 1) yes 2) no
If yes, continue.
2.1 At what age did you start to smoke? wife:_____ husband:_____
2.2 At what age did you quit smoking for the first time? wife:_____ husband:_____
2.3 At what age did you quit smoking for the last time? wife:_____ husband:_____
2.4 How many months have you quit smoking? wife:_____ husband:_____

3. The Kinds and Amount of Tobacco

3.1 For wife:

Kinds of tobacco _____
# of cigarettes per day _____
Year starting smoking __/__/__ (M/D/Y)
Year quit smoking __/__/__ (M/D/Y)
Years of smoking _____ yrs

3.2 For husband:

Kinds of tobacco _____

# of cigarettes per day _____

Year starting smoking __/__/__ (M/D/Y)

Year quit smoking __/__/__ (M/D/Y)

Years of smoking _____ Yrs

VI. Alcohol Consumption

1. At present, do you often drink alcohol? Y/N wife:_____ husband:_____
   (if no, go to 2; if yes, go to 1.1 1.2, then skip to 3)
   1.1 What age did you develop this habit of drinking alcohol? wife:_____ husband:_____
   1.2 What kind of alcoholic beverage do you often drink?

For wife:

Kind of alcoholic beverage	1) ___liquor	2) ___beer	3)___wine	4)___others
Times per week	1) _____	2) _____	3) _____	4) _____
# of Liangs/bottles each time	1) _____	2) _____	3) _____	4) _____

For husband:

Kind of alcoholic beverage	1) ___liquor	2) ___beer	3)___wine	4)___others
Times per week	1) _____	2) _____	3) _____	4) _____
# of Liangs/bottles each time	1) _____	2) _____	3) _____	4) _____

2. Have you ever had a habit of drinking alcohol? Y/N wife:_____ husband:_____
   (if no, go to 3; if yes, go to 2.1-2.3)
   2.1 At what age did you start this habit? wife:_____ husband:_____
   2.2 What kind of alcoholic beverage did you often drink? wife:_____ husband:_____
   2.3 What are the major reasons for giving up drinking? 0.

wife:_____ husband:_____

1)disease or sickness 2) family objection 3) economic reasons 4) recognition the hazardous effects of drinking alcohol 5) other

3. Have you ever been drunk? Y/N wife:_____ husband:_____
   3.1 When was the last time you got drunk? wife:_____ husband:_____

VII. Drinking Tea

1. Do you have a habit of drinking tea? wife:_____ husband:_____
   (if no, go to IX.)
   1.1 When did you develop this habit? wife:_____ husband:_____
   1.2 How many years has it been since you had this habit? wife:_____ husband:_____
   1.3 What do you often prefer to drink: wife:_____ husband:_____
   1) light tea 2) medium tea 3) strong tea
   1.4 How many times a day do you make new cups of tea?
   wife:_____ husband:_____
   1.5 How much tea do you drink on average each month (in liang)? wife:_____ husband:_____
   (1 liang=500 grams)
   1.6 What kind of tea do you often drink? wife:_____ husband:_____
   1) jasmine tea 2) green tea 3) black tea

VIII. Menstrual History (For Female)

1. How old were you when you began to menstruate? _____ yrs
2. During the past year, were your menstrual periods regular? Yes/No
3. How many times have you had a menstrual period during the past 12 months (a year)?
   3.1 On the average, how many days do you bleed? _____ days
   3.2 What is your longest period? _____ days
   3.3 What is your shortest period? _____ days
   3.4 Generally, how many days does your menstrual period last?

4a. Your latest menses started on ____ month____ day
4b. How many days did this menstrual period last?
5a. Your menses of the time before last started on _____month _____day
5b. How many days did that menstrual period last?

6. Did you ever have any vaginal bleeding between menstrual periods?
1) never 2) occasionally 3) often

7. Do you experience any of the following symptoms during your menses?
1) dysmenorrhea 2) backache 3) somnolence 4)easily tired 5) mood upset
6) headache 7) nausea 8) vomiting 9) others (note, please)_____

8. What contraceptive methods do you use?
1) condom 2) oral drugs 3) IUD 4) others

8a. Did you ever take any contraceptive medicine?
if yes, list the drug name_____ amount_____
duration of taking this drug, from ____/____(M/Y) to ___/___(M/y)

9. Have you ever been pregnant?
9a. if yes, what was the outcome of this pregnancy
1) spontaneous abortion _____ date ___/___ (M/Y)
2) induced abortion _____ date ___/___ (M/Y)
3) live birth_____ date ___/___ (M/Y)
4) still birth _____ date ___/___ (M/Y)
5) deformity _____ date ___/___ (M/Y)
6) others (note, please)_____ date ___/___ (M/Y)

10. In the past year, have you had repeated bouts of:
a) Vaginal itching _____yes _____no
b) Vaginal ulcer _____yes _____no
c) Excessive vaginal discharge _____yes _____no
IF YES: i)Foul Smelling _____yes _____no
ii)White, no odor _____yes _____no

11. In the last year, have you had the experience of burning upon urination?
_____yes _____no

12. (For both male and female)
12.1 Have you ever tried to conceive for more than 12 months but did not become pregnant?
_____yes _____no
IF YES: From _____/_____ (M/Y) To _____/_____ (M/Y)
12.2 Have you ever visited a doctor for infertility problems?
_____yes _____no
IF YES: Year, months _____

IX. Family History
1. How many times has your mother been pregnant?
Of those pregnancies, how many resulted in:
1) Normal birth _____
2) Spontaneous abortion _____
3) Birth deformity _____
4) Pre-term birth _____
5) Low-birth weight _____
6) Still birth or fatal death _____

7) Induced abortion _____

X. Home Environment

1. When did you both start living together? ___/___(M/Y)
2. How many rooms do you have in your house?
3. How large is your living space? _____square meters
4. Type of house:
   1) a multi-story building, # of floors_____
   2) a single-story house (code 60)
   3) other (code 70)
5. Location of your house:
   5.1 Is there any factory near your house?
   name of the factory _____
   5.2 How far is your house from to this nearby factory _____meter
   5.3 Direction of the factory site from your house _____
   1) east 2) northeast 3) north 4) southwest 5) west
   6) northwest 7) north 8) northeast
   5.4 Is your house near any traffic road or railroad? 1)no 2) yes ____
6. Is there any air conditioning in your house? 1)no 2) yes ____
7. Is your bedroom separate from your kitchen? 1)no 2)yes ____
8. Is there any fan or smoke ventilation in your kitchen? 1)no 2) yes ____
   if yes, how frequent do you use this fan? _____
   1) very often 2) occasionally 3) seldom
9. What fuel is used most often for cooking in your home:
   name of fuel (use code,please) _____, _____
   amount of fuel (kg per month) _____, _____
10. During your cooking, your kitchen has:_____
    1) almost no smoke 2) a little smoke(not choke causing) 3) a lot of smoke (choke causing)
11. During your cooking, your bedroom has:_____
    1) almost no smoke 2) a little smoke(not choke causing) 3) a lot of smoke (choke causing)
12. Do you often cook? _____
    1) often 2) seldom 3) never
13. How is your home heated in winter? _____
    1) central heating system 2) coal stove 3) self-made heating system
    2) other
    if you use a coal stove,
    13a. How much coal do you need every winter?
    Kg of coal per year _____
    13b. Where is your stove located in your house?
    1) in bedroom 2) in living room 3) other
    13c. Is there any chimney with your stove(s)?
14. Are there any people who live with you who smoke? 1)no 2)yes _____
    if yes,
    14.1 How many people smoke? _____
    14.2 How many cigarettes do they smoke every day ? #_____
15. Do you feed any pet or animal? 1) no 2) yes IF YES:
    15.1 please list the code(s) of your pet or animal ____,____,_____

16. Socio-Economic Status of Relatives

For Women:

Relative	Institute	Occupation	Job Title	Category	Income
Grandfather					
Grandmother					
Father					

Mother
Brothers
Sisters
Uncles
Aunts
Brothers-in-law
Sisters-in-law

For Men:

Relative	Institute	Occupation	Job Title	Category	Income
Grandfather					
Grandmother					
Father					
Mother					
Brothers					
Sisters					
Uncles					
Aunts					
Brothers-in-law					
Sisters-in-law					

XI. Diet Pattern

1=(Yes) 2=(No)

1.On average, how many times a week do you eat your meals outside of your home? |__|__|
2.Do you eat at regular times? 1=No 2=usually 3=strictly |__|
3.Do you eat the same amount of food each day? 1=Not the same 2=about the same 3=same |__|
4.How fast do you eat? 1=Very slowly 2=about average 3=fast 4=very fast |__|
5.What kind of food do you prefer? 1=cold 2=warm 3=hot 4=very hot |__|
6.How many meals do you eat each day? |__|
7.How many times do you eat breakfast each week? |__|
8.What kind of meat do you eat 1=do not eat 2=mainly lean meat 3=half lean, half fatty 4=mainly fatty meat |__|
9.How many days does it take you to consume 500g of salt? |__|__|__|
10.How many days does it take you to consume 500g of soy sauce? |__|__|__|
11.How many days does it take you to consume 500g of sugar? |__|__|__|
12.Do you like to add more salt to your dishes, noodles, dumplings, and/or won tons? |__|
13.Do you like to add more soy sauce to your dishes, noodles dumplings and/or won tons? |__|

14.What kind of taste do you like?: 1=sour 2=hot 3=sweet 4=salty 5=light 6=bland
15.Do you like to eat uncooked and hard food? 1=No 2= Yes
16.Where do you store your food in the summer? 1=refrigerator 2=in a pot 3=in a bowl |__|
17.How many meals are the leftover from the previous day each week? |__|
1=none 2=1-2meals 3=3-4meals 4=5 or more meals
18.Do you heat your leftover before eating them? |__|
1=never 2=occasionally 3=often 4= always
19.How do you deal with mildewed vegetables and fruits? |__|
1=throw away 2=cut off the mildewed part and eat the rest, 3=wash out the mildewed part and eat the rest
20.How do you dealing with mildewed rice and cakes? |__|
1=throw away 2=cut off the mildewed part and eat the rest 3=wash out the mildewed part and eat the rest
21.Would you eat the following mildewed food?
21.1 a little bit sour with an odor 1=Never 2=occasionally 3=often |__|
21.2 very sour with an odor 1=Never 2= occasionally 3=often eat |__|
22. Does your stored food ever become mildewed? |__|
If Yes,**22.1How frequently?** 1=not very often 2=some times 3=every year |__|

23.How do you deal with the following mildewed stored food?: **If do not have, use "1"**
1=do not eat them 2=place in the sun shine, get rid of the mildewed part and eat the rest
3=eat as is

23.1 Mildewed corn |__|
23.2 Mildewed peanut |__|
23.3 mildewed wheat |__|
23.4 mildewed rice |__|

24. Have you changed your dietary habits within the last 15 years? |__|
If yes, 24.1For what reason have you changed your diet?_____
24.2At what age did you change your diet? |__|__|
years old

25.What kinds of vegetables do you eat the most?:_____ _____ _____ _____

Have you eaten the following foods within the last year?

E1 Main food (One bowl=100g	Do not eat	Per month <1time	Per Month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
rice									
millet									
wheat food (bread, cake)									
corn									
sorghum									
sweet potato									
Deep fried pastry									
Other (Steamed bun, dumplings) (Please list in detail)									
E2 Meat and sea food (one bowl=100g)	Do not eat	Per month <1time	Per Month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
lean pork									
fatty pork									
beef									
lamb									
chicken									
duck									
liver									
other organs									
sausage									
cured meat									
other meat products(meat pulp, chashao pork)									
all sea food									
fresh fish									
smoked fish or meat									
shrimp									
crab									
shell food									
salty fish									
kelp									
dried laver									
dried shrimp									
E3milk products	Do not eat	Per month <1time	Per Month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
whole milk(cup)									

low fat milk(cup)									
whole milk powder(spoon)									
low fat milk powder(spoon)									
lamb milk(cup)									
cheese(one piece)									
yogurt									
ice cream (one piece)									
other milk products(cup)									
E4 eggs	Do not eat	Per month <1time	Per Month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
chicken eggs									
other eggs									
pickled eggs									
duck eggs									
E5 oil	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
all oil									
peanut oil									
corn oil									
bean oil									
vegetable oil									
cottonseed oil									
animal oil									
E6 bean curd products (one bowl =100g)	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
bean curd									
bean curd soup									
bean curd milk									
dried bean curd									
soy bean									
mung bean									
bean sprouts									
other bean products									
E7pickled foods	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
pickled sour vegetables									
pickled salty vegetables									
mashed bean vegetables									
fermented soy bean curd(piece)									
paste-like fermented mashed bean									
hot fermented mashed bean									
hot oil									
self made pickled vegetables									
E8 snacks (bowl)	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
cakes									
crackers									
chocolate									

other candy									
other nut (peanut, seeds) (cup)									
E9 Beverages	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
mild liquor (100g)									
strong liquor (100g)									
beer(bottle)									
wine(100g)									
coffee(cup)									
E10 tea(cup)	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
all kinds of tea									
green tea									
red tea									
flower tea									
other									
E11vegetables(bowl)	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
all fresh vegetables									
spinach									
all other green vegetables									
bean									
green cauliflower									
white cauliflower									
celery									
green bell pepper									
red bell pepper									
yellow bell pepper									
tomato									
radish									
other red and yellow vegetables									
Napa cabbage, cabbage									
eggplant, cucumber									
potato									
mushroom									
onion									
green onion									
pepper									
garlic(piece)									
balsam pear									
wild vegetables									
other									

E12 fruits	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
banana(one)									
water melon(slice)									
cantaloupe(one)									
apple(one)									
pear(one)									

orange(one)									
grape(bowl)									
peach(one)									
jujube(bowl)									
muskmelon(one)									
strawberry(one)									
apricot(one)									
plum(one)									
persimmon(one)									
all pickled fruits(bowl)									
orange juice(cup)									
other juice(cup)									
dried grape(bowl)									
other dried fruits(bowl)									
haw tree fruit(one)									
wild fruits(one)									
E13vitamin	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times
Multiple vitamin(tablet)									
vitamin C(tablet)									
vitamin A(tablet)									
vitamin D(tablet)									
vitamin E(tablet)									
cod-liver-oil(tablet)									
vitamin B(tablet)									
vitamin B1(tablet)									
vitamin B2(tablet)									
vitamin B6(tablet)									
vitamin B12(tablet)									
folic acid(tablet)									
chalybeate									
zincoid									
calcium tablet(tablet)									
aspirin									
trace element									
other medicine of care									
E14 other frequently eaten foods	Do not eat	Per month <1time	Per month 1-3 times	Per week 1-2 times	Per week 3-4 times	Per week 5-6 times	Per day 1time	Per day 2-3 times	Per day >=4 times

Signature of Interviewer:_____

Date of Interviewing: ___/___/___ (M/D/Y)

Signature of Inputter: _____

Date of Input: ___/___/___ (M/D/Y)

Appendix I-3:

BEGINNING QUESTIONNAIRE
REPRODUCTIVE HEALTH SURVEY
(For Women only)

IDENTIFICATION

Subjects' Names: Wife's _____

Social Security ID: Wife's _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

SURVEY PROCESS

Times of Visit	Date of Visit	Result of Visit			Interviewer's Name
		Refused	Absence	Finished	
First visit					
Second visit					
Third visit					

RESULTS - FORM REVIEW

Times of Form Review	Date of Form Review	Quality Comments			Examiner's Name
		Passed	Revised	Invalid	
First time					
Second time					
Third time					

Signature of Form Re-examiner:_____

1. When do (did) you begin to complete the "Women's Health Study Diary"?

____/____/____(MDY)

2. When did you get married? ____/____/____ (MDY)
3. When did you get childbirth permission? ____/____/____ (MDY)
4. When did you begin attempting to conceive? ____/____/____(MDY)
5. Did you use any contraceptive method in the last month? Yes___ No___
6. If yes, what contraceptive method did you use?
   Condom___ oral contraceptives____ IUD ___ rhythm method____
   Extravaginal ejaculation ____ others(specify)_____

7. Please check all the contraceptive methods you ever used(currently or before) and the time period each was used.

Method	From	To
Condom	Year_____ month_____	Year_____ month_____
Oral contraceptives	Year_____ month_____	Year_____ month_____
IUD	Year_____ month_____	Year_____ month_____
Rhythm method	Year_____ month_____	Year_____ month_____
Extravaginal ejaculation	Year_____ month_____	Year_____ month_____
Other	Year_____ month_____	Year_____ month_____

8. Your last menstruation started on ___/___/___(MDY)
9. During the last menstruation, did you experience dysmenorrhea? Yes__ no___
10. During the last month, how many times have you had sexual intercourse? ____
11. When did you stop using contraception? ____/____/_____(MDY)
12. During the last month, did you experience the following situations?
    Long hours of standing: Yes__ No___
    Long hours of bending or squatting: Yes__ no___
    Long hours of overloading on shoulder: Yes__ no___
    Falling: Yes__ no___
    Exposure to strong vibrations: Yes__ no___
    Acute dust exposure (emergency case) : Yes__ no___
    Exposure to loud noise: Yes__ no___

The following questions refer to the time period since the last survey:

I. General Health Status

a. # of Diseases

01 varicella & herpes zonstic
02 nettle rash
03 tuberculosis
04 parotitis
05 asthma
06 bronchitis
07 pneumonia
08 flu
09 other respiratory diseases
21 diabetes
22 hyperthyroidism
23 hypothyroidism
24 anemia
25 other blood diseases
26 hereditary diseases
27 Bobor's bacillus disease
28 other insect-transferred diseases
29 malignant tumors

10 hypertension
11 coronary heart disease
12 immune system disease
13 congenital heart disease
14 myocardium diseases
15 other heart diseases
16 hepatitis
17 stomach & duodenal ulcer
18 cholecystitis
19 nephritis
20 pyelonephritis

30 cervical polyp
31 perineum tumor
32 vaginitis
33 cervicitis
34 myoma of uterus
35 sleep disorders
36 carcinoma of cervix
37 prolapse of uterus
38 irregular menstruation
39 carcinoma of uterus body
40 tumors of ovary
41 pelvic inflammatory disease
42 tumor of breast
43 others

b. Hospital of Diagnosis
1. hospital directly administrated by central government, municipal government and all ministries of the government
2. hospital at regional or provincial level
3. hospital at district or county level
4. hospital for primary care and hospital at township level
5. primary care post or private clinic

c. Outcome of disease
1. cured 2.improved 3.no change 4.degenerated

1.1 Have you been suffering from any of the above diseases which were diagnosed by your doctor?
Yes___ No___ Disease #___, #___, #___, other_____
Hospital #___, #___, #___ _____
Outcome #___, #___, #___ _____

1.2 If yes, do you take medicine currently? (please see drug # appendix)
Yes___ No___ Drug #___, #___, #___, other_____

1.3 Could you tell me your weight and height?
height_____ (cm)
weight_____ (kg)
weight at birth_____(kg)

1.4 Have you been hospitalized since last survey? ____
1.never 2.yes
If yes, 1.4.1 How many times have you been hospitalized?_____
1.4.2 When was your last time in the hospital?
__/__/__(M/D/Y)
1.4.3 What was the reason? _____

1.5 Have you suffered from sleep disorders since last survey?_____
1. never 2.yes
If yes, 1.5.1 What type?_____
1.5.2 How many times a week did this effect you?_____

1.6 How long does it take you to fall asleep? _____

II. Occupation

1. Did you change your job since the last survey? Y/N_____
   If yes, continue. If no skip to 1.5

1.1 Name of your plant _____
Name of your workshop_____
Name of your specific area_____
Name of your job title_____
Job salary range_____

1.2 When did you begin this job? ___/___ (M/Y)

1.3 When did you end your last job? ___/___ (M/Y)

1.4 How long have you had this job? _____months

1.5 How many hours a week do you work at your present job? _____hours

1.6 Do you come into contact with any kind of toxic substances? Y/N_____
(if no, go to 1.7)

1.6.1 Name of the major toxic substance in daily work (please use code) _____
_____
_____

1.6.2 Hours of daily contact with toxic substance: _____

1.6.3 Are there any protective measures taken? _____
1. no 2. gauze mouth mask 3. gloves 4. gas mask
5. gloves+gauze mouth mask 6. gloves+gas mask 7. others

1.6.4 The concentration of the toxic substances is:_____
1. low 2. medium 3. high

1.7 Do you come into contact with dust in your daily work? Y/N_____
(if no, go to 1.8)

1.7.1 Name of the major dust (please use code) :_____

1.7.2 Hours of daily contact with dust:_____

1.7.3 Concentration of the dust that you contact is: _____
1. low 2. medium 3. high

1.7.4 Are there any protective measures taken?_____
1.not any 2.gauze mouth mask
3.dust mouth mask or mask set 4. others

1.8 Are you exposed to noise in your daily work? Y/N_____
(if no, go to 1.9)

1.8.1 Hours of daily exposure to noise:_____

1.8.2 Degree of noise in your work:_____
1. light 2. medium 3. heavy

1.8.3 Are there any measures for the noise protection taken? Y/N_____

1.9 Are you exposed to vibration in your daily work? Y/N____
(if no, go to 2)

1.8.1 Vibration effects:_____

1. whole body 2. local part(s) of body
1.8.2 Hours of daily exposure to vibration:_____
1.8.2 Degree of the vibration in your work:_____
1. light 2. medium 3. heavy

2. What is the major position you use in your daily work?:_____
1. sitting 2. standing (in the same place)
3. bending 4. squatting or kneeling 5. mobile 6.others
2.1 How many hours do you remain in these positions?
position 1._____ position 2._____ position 3._____
position 4._____ position 5._____ position 6._____

3. How often do you need to lift or move heavy goods in your job? _____
1. never 2. sometimes 3. always

4. What is the level of physical exertion in your job? _____
1. light 2. medium 3. heavy

5. What is your work shift?_____
1. day shift 2.night shift 3. 2-shift
4. 3-shift 5. 4-shift
6. The temperature in your workplace often is:_____
1. normal room temperature 2. high temperature
3. low temperature

7. The humidity in your workplace often is:_____
1. normal room humidity 2. dry 3. moist

8. Is there any air conditioning at your workplace? Y/N:_____

9. How stressed do you feel at your workplace?_____
1. not very 2. a little 3. very

10.Do your colleagues in your office or work room smoke while they are on duty? (if no, go to 11) Y/N_____
10.1 How many smokers are in your office/work room?_____
10.2 About how many cigarettes do they smoke every day?:_____

11. How large is your office? (square meters):_____

12. How is your workplace heated?_____
1. central heating system 2. coal stove 3. others
(if answer 1 or 3 item, go to III.)
12.1 Is there a chimney with your coal stove? Y/N:_____
12.2 How much coal is burned each year? (Kg):_____

III. Daily Physical Activities

1. What kind of transportation do you take to your office?:_____
1. walking 2. bicycle 3. bus or shuttle 4. car 5. other

2. How far is from your home from your office?:_____
   1. <500m 2. 500m- 3. 1Km- 4. 5Km- 5. 10Km & over

3. How do you consider the stress level of your work?_____
   1. not stressful 2. average 3. very stressful

4. How many hours do you spend doing housework?_____

5. How often do you play sports?_____
   1. more than once a day 2. 4-6 times a week 3. 1-3 times a week
   4. 1-4 times a month 5. less than once a month

   5.1 What is the level of physical exertion during exercise?_____
   1. light (daily activities)
   2. medium (heart beating after the activities)
   3. serious (sweating after the activities)

V. Diet Pattern

1. What kind of cooking oil do you most often use? _____
   1. only plant oil 2. mostly plant oil 3. mostly animal oil

2. Do you often eat fatty meat or lean meat?_____
   1) mostly fatty meat 2) mostly lean meat 3) half fatty half lean

3. What is the amount of the meat you eat each week?_____
   1) less than 0.25kg 2) 0.25-1 kg 3) more than 1kg 4) vegetarian

4. Do you often eat eggs?_____
   1) never 2) less than two a week 3) 3-7 a week 4) more than 7 a week

5. Do you often drink milk?_____
   1) never or occasionally 2) about 0.25kg a day 3) about 0.5 kg a day
   4) above 0.5kg a day
6. Do you often eat fish?_____
   1) never or occasionally 2) about 0.25 kg a week 3) about 0.5 kg a week
   4) above 0.75 kg a week
7. Do you often eat tofu products?_____
   1) never or occasionally 2) about 0.25kg a week 3) about 0.5kg a week
   4) above 0.75 a week

8. Do you often eat vegetables?_____
   1) occasionally or 0.1kg a day 2) 0.1-0.25kg a day 3) 0.25-0.5kg a day
   4) above 0.5kg a day

9. Do you often eat carrots or green leafy vegetables?_____
   1) occasionally 2) eat seasonally 3) often eat during the whole year

10. Do you often take the following vitamins?_____

1) vitamin A 2) vitamin B 3) vitamin C 4) vitamin E 5) multiple vitamin
6) do not take vitamins

11. Do you prefer foods to be salty or light?_____
    1) prefer salty 2) prefer light
12. Do you often eat thick bean sauces, pickled vegetables, and/or pickled foods?_____
    1) do not often eat 2) often eat

VI. Smoking Status

1. Have you smoked since the last survey? _____
    1) yes 2) no
    If no, go to VI; If yes, continue.
  1.2 How many cigarettes do you smoke every day? _____
  1.3 Generally, how far do you draw smoke to your body?_____
    1) into the mouth 2) into the throat 3) into the lungs
  1.4 Have you reduced the amount of smoking within the last year?_____

  1.4.1 Why did you reduce the amount of smoking? _____
    1) disease, disease name (code) _____
    (2) economic reason (3) objection from family members
    (4) recognition of the hazardous effects of smoking (5) others

2. The Kinds and Amount of Tobacco

2.1

Kinds of tobacco	
# of cigarettes per day	_____
Year starting smoking	___/___(M/D)
Year quit smoking	___/___(M/D)
Years of smoking	_____YRS

VII. Alcohol Consumption

1. Have you often drunk alcohol since the last survey? Y/N _____
   (if no, go to 2; if yes, go to 1.1, then skip to 3)
  1.1 What kind of alcoholic beverage do you often drink?

Kind of alcoholic beverage	1) ___liquor	2) ___beer	3)___wine	4)___others
Times per week	1) _____	2) _____	3) _____	4) _____
# of Liangs/bottles each time	1) _____	2) _____	3) _____	4) _____

2. Have you ever had a habit of drinking alcohol since the last survey? Y/N _____
   (if no, go to 3; if yes, go to 2.1,2.2)
  2.1 What kind of alcoholic beverage did you often drink? wife:_____husband:_____
  2.2 What are the major reasons for giving up drinking? wife:_____ husband:_____
    1)disease or sickness 2) family objection 3) economicreasons
    4) recognition of the hazardous effects of drinking alcohol 5) other

3. Have you ever been drunk since the last survey? Y/N: _____
  3.1 When was the last time you got drunk? _____

VIII. Drinking Tea

1. Do you have a habit of drinking tea? _____
   (if no, go to IX.)

1.1 Did you develop this habit since the last survey? _____
1.2 Do you often prefer to drink: _____
1) light tea 2) medium tea 3) strong tea
1.4 How many times a day do you make new cups of tea? _____
1.5 How many liangs of tea do you drink each month? _____
1.6 What kind of tea do you often drink? _____
1) jasmine tea 2) green tea 3) black tea

IX. Menstrual History

1. How many times have you had a menstrual period since the last survey?_____
1.1 On the average, how many days do you bleed? ____days

2a. Your latest menses started on ____month____day
2b. How many days did this menstrual period last?--------
3a. Your menses of the time before last started on _____month _____day
3b. How many days did that menstrual period last?_____

4. Have you ever have any vaginal bleeding between menstrual periods since the last survey?_____
1) never 2) occasionally 3) often

5. Have you experienced any of the following symptoms during your menses since the last survey?_____
1) dysmenorrhea 2) backache 3) somnolence 4)easily tired 5) mood upset
6) headache 7) nausea 8) vomiting 9) others (note, please)_____

6. Have you been using any contraceptive methods since the last survey?_____
6.1 If yes, which?:_____
1) condom 2) oral drugs (include name) 3) IUD 4) others

7. Have you been pregnant since the last survey?_____
7a. if yes, what was the outcome of this pregnancy?_____
1) still pregnant
2) spontaneous abortion _____ date ___/___ (M/D)
3) induced abortion _____ date ___/___ (M/D)
4) live birth _____ date ___/___ (M/D)
5) still birth _____ date ___/___ (M/D)
6) deformity _____ date ___/___ (M/D)
7) others (note, please) _____ date ___/___ (M/D)

8. Since the last survey, have you had repeated bouts of:
a) Vaginal itching _____yes _____no
b) Vaginal ulcer _____yes _____no
c) Excessive vaginal discharge _____yes _____no
IF YES: i)Foul Smelling _____yes _____no
ii)White, no odor _____yes _____no

9. Since the last survey, have you had the experience of burning upon urination?
_____yes _____no

X. Home Environment

1. What fuel is used most often for cooking in your home:
   name of fuel (use code,please) _____, _____
   amount of fuel (kg per month) _____, _____
2. During your cooking, your kitchen has:_____
   1) almost no smoke 2) a little smoke(not choke causing) 3) a lot of smoke (choke causing)

3.During your cooking, your bedroom has:_____
   1) almost no smoke 2) a little smoke(not choke causing) 3) a lot of smoke (choke causing)

4. Do you often cook? _____
   1) often 2) seldom 3) never

5. Has your home been heated since the last survey? Y/N _____
   If yes, how?_____
   1) central heating system 2) coal stove 3) self-made heating system
   4) other
   if you use a coal stove,
   5a. How much coal did you use since last survey ?
   Kg of coal _____
   5b. Where is your stove located in your house?
   1) in bedroom 2) in living room 3) other
   5c. Is there any chimney with your stove(s)?

6. Are there any people who live with you who smoke? 1)no 2)yes _____
   if yes,
   6.1 How many people smoke? _____
   6.2 How many cigarettes do they smoke every day ? #_____

7. Do you feed any pet or animal? 1) no 2) yes IF YES:
   7.1 please list the code(s) of your pet or animal ____,____,_____

Signature of Interviewer:_____
Date of Interview: ___/___/___ (M/D/Y)
Signature of Input person: _____
Date of Input: ___/___/___ (M/D/Y)

ID

REPRODUCTIVE HEALTH STUDY (Daily Diary)

NOTE: Every woman is unique / Each day's entry is important

DATE OF THE MONTH	
DAY OF THE WEEK	

TODAY *(Midnight yesterday to Midnight tonight):*		
1.When did you collect the urine sample? (1=1st urine after awakening; 2=later; 0=not collected)		
2.How many hours have lasted since the most previous urination until the time of urine collection?		
3.Did you experience any of the following symptoms today?		
3a.Nausea (0=no; 1=yes)		
3b.Bloating or weight gain (0=no; 1=yes)		
3c.Headache (0=no; 1=yes)		
3d.Mood change (irritability, depression, anxiety) (0=no; 1=yes)		
3e.Breast tenderness (0=no; 1=yes)		
3f.Menstrual (period) cramps? (0=no; 1=yes)		
If Yes	3g.How severe? (1=mild; 2=severe; 3=very severe)	
If Yes	3h. Did you take pain relief medicine? (0=no;1=yes)	
4.Did you have menstrual (period) bleeding today? (0=no; 1=yes)		
If Yes	4a. How many sanitary napkins did you use? (0=none)	
If Yes	4b.When did it begin? (1=this morning; 2=later today; 3=last night; 4=yesterday; 5=before yesterday)	
4c.Was this your regular menstrual bleeding? (0=no; 1=yes)		
5.Did you have sexual intercourse? (0=no; 1=yes)		
If Yes	5aWhat type of birth control method did you use (write in all that apply)? (0=none 1=condom 2=birth-control pills 3=rhythm/withdrawal 9=other)	
6.Did you have a cold, flu, or other infections? (0=no; 1=yes)		
7.Did you have a fever? (0=no; 1=yes)		
7a.Did you take any drugs (prescription, non-prescription or recreational)? (0=no; 1=yes)	7b.What drugs did you take? (DK=don't know)	
If Yes		
8. How much of the following items did you take yesterday?		
8a.# cigarettes (0=none)		
8b.# drinks alcohol (include beer, wine, cooking wine, liquor) (0=none)		
8c.# cups caffeinated coffee (0=none)		
8d.# cups non-herbal tea (0=none)		
8e.# cans/bottles caffeinated soda drinks (0=none)		
8f.# cups other drinks or fluids, including water, porridge, noodle soup, other beverages (0=none)		
9.Was there anyone who smoked around you yesterday?		
9a.At home: total # of cigarettes smoked around you (0=none)		
9b.At workplace: total # of cigarettes smoked around you (0=none)		
10.How many minutes did you spend doing vigorous exercise? (0=none)		
11.Did you go to work today? (0=no; 1=yes)		

PLEASE TURN CARD OVER TO SIDE 2.

TODAY *(Midnight yesterday to Midnight tonight)*

DAY OF THE WEEK	
12.When did you get up (write in hours and be sure to include "A" for A.M. or "P" for P.M.)?	
13.When did you go to sleep (write in hours and be sure to include "A" for A.M. or "P" for P.M.)?	
14.What were the total number of hours that you worked?	
15.How many hours did you spend at work doing each of the following:	
15a.# hours sitting (0=none)	
15b.# hours spent standing on your feet (0=none)	
15c.# hours watching TV(0=none)	
15d.# hours bending or squatting(0=none)	
15e.# hours overloaded on shoulder(0=none)	
16.Did you experience any of the following situations yesterday?	
16a.falling (0=no; 1=yes)	
16b.quarrel or fight with other person(s) (0=no; 1=yes)	
16c.exposure to strong vibrations (0=no; 1=yes)	
16d.acute dust exposure (emergency case) (0=no; 1=yes)	
16e.exposure to loud noise (0=no; 1=yes)	
17.Did you experience any unschedule events yesterday? Y/N.	
If Yes	
17a. Brief description of the event:	
17b. Duration at the location _____ hour_____minute.	
17C. Skin contact with Chemical: _____ Y/N	
17d. Use of personal protection equipment:_____	
17 e. possible chemicals of exposure _____	

Primary Form Examiner(clinic)_____ Final Form Examiner(health station)_____

Appendix I-5:

Questionnaire at the End of the Women's Health Study

ID:_____ Date of Birth: ____/____/____(MDY) Today's date: ____/____/____(MDY)

1. When do(did) you begin recording the "Newly Married Women's Health Study Diary"?

____/____/____(MDY)

2. When was the last day of the diary? ____/____/____(MDY)
3. What was the reason for you to stop recording the diary?
   1.Pregnancy 2. Gynecological illness 3. Other illness_____
   4. Other reason _____
4. Your latest menstruation started on ___/___/___(MDY)
5. During the latest menstruation, did you experience dysmenorrhea? Yes__ no___
6. How many times of menstruation have you had since you began recording your daily diary?

____

The following questions refer to the period of daily diary collection

During your daily diary collection period:

7. What was your longest period? _____
8. What was your shortest period? _____
9. Did your have any vaginal bleeding between menstrual periods? Yes____ No____
10. Did you experience any of the following symptoms during your menses?
    1. dysmenorrhea 2. Backache 3. Somnolence 4. Easily tired 5. Mood upset
    6. headache 7. Nausea 8. Vomiting 9. Others (specify)_____
11. Did you use any contraceptive method last month? Yes___ No___
12. If yes, what contraceptive method did you use?
    Condom___ Oral Contraceptives____ IUD ___ Rhythm Method____
    Extravaginal ejaculation ____ others(specify)_____

13. Did you experience the following situations:

Long hours of standing:	Yes__ No___
Long hours of bending or squatting:	Yes__ no___
Long hours of overloaded on shoulder:	Yes__ no___
Falling:	Yes__ no___
Exposure to strong vibrations:	Yes__ no___
Acute dust exposure (emergency case) :	Yes__ no___
Exposure to loud noise:	Yes__ no___

Appendix I-6:

Missing Diary Card

ID:_____

1.Today's date: ____/____/____(MDY)

2. How many days did you stop recording the diary? _____ days

3. What was the reason for you to stop recording the diary?_____
   1. Illness 2. Busy with job 3. Continuing education
   4. On vacation 5. Absent 6.Other reason _____

4. Did you have menstrual bleeding during those days? (0=no; 1=yes)
   if yes
   4a. Was this your regular menstrual bleeding? (0=no; 1=yes)
   4b. Have you experienced any of the following symptoms during your menses ?
   1) dysmenorrhea 2) backache 3) somnolence 4)easily tired 5) mood upset
   6) headache 7) nausea 8) vomiting 9) others (note, please)_____

5. Did you have sexual intercourse during those days? (0=no; 1=yes)
   if yes
   5a. What type of birth control method did you use (write in all that apply)?
   1=none 2=condom 3=birth-control pills
   4=rhythm/withdrawal 5=other

6.Did you experience any unscheduled events during those days? Y/N.
   if yes
   17a. Brief description of the event: _____
   17b. Duration at the location _____ hour_____minute.
   17C. Skin contact with Chemical: _____ Y/N
   17d. Use of personal protection equipment:_____
   17 e. possible chemicals of exposure _____

Appendix I-7:

Daily Urine Collection Registration Card

Wife: ID__________ Name ________

Date	Wife	Receiver/time	Pick-up person/time	Notes

Appendix I-8:

Questionnaire for subjects who withdraw from the Study

ID:_____

1. What's your plant and workshop? Plant _____ Workshop _____.

2.Today's date: ____/____/____(MDY)

3. When do(did) you begin keeping a diary for the "Women's Health Study"?

____/____/____(MDY)

4. When was the last day of the diary? ____/____/____(MDY)

5. What was the reason for you to stop recording the diary?

1. Illness 2. Change to another unit 3. Continuing education
4. Busy with job 5. Absent 6.Other reason _____

RESEARCH GRANT NO. 5RO1 OH03027-04 (PETROCHEMICAL EXPOSURES AND REPRODUCTIVE OUTCOMES)

ITEM	COST	%	CONDITION	RETAIN	SERIAL	DATE
COMPUTER DESKTOP	$2,089.37	0.22%	OBSOLETE	Y	CPQ198340002	02/19/94
DYNATECH(HONG KONG)LIMITED	$8,500.00	0.88%	FAIR	Y	G4741	08/16/94
FREEZER	$9,176.00	0.95%	FAIR	Y	1799156	09/03/94
GILIAN INSTRUMENT GILBRATOR	$1,548.33	0.16%	FAIR	Y	800508111	01/17/95
GILIAN INSTRUMENT GILBRATOR	$926.50	0.10%	FAIR	Y	8002712	02/02/95
BIOLINX SOFEWARE	$800.00	0.08%	FAIR	Y	016-010-0200	05/20/95
FREEZER	$1,387.96	0.14%	FAIR	Y	24041	12/04/95
SURVEY SPIROMETER	$6,905.50	0.72%	FAIR	Y	1139,1140+1141	01/25/96
PRINTER HP	$520.00	0.05%	FAIR	Y	USCB042750	03/02/96
COMPUTER DELL	$3,432.74	0.36%	FAIR	Y	89184	03/15/96
COMPUTER DELL	$1,813.25	0.19%	FAIR	Y	89185	03/15/96
EMAX FITR IN ORIG CAT NBR	$7,133.03	0.74%	FAIR	Y	2000300	04/24/96
COMPUTER	$985.37	0.10%	FAIR	Y	2688	04/30/96
FOUNTAIN TECH	$1,180.95	0.12%	FAIR	Y	IN410-850T1	05/01/96
FR2R ISTM ULTLW	$6,712.00	0.70%	FAIR	Y	Q6110-1107-21	05/15/96
INC.THERM CONDUC.	$2,999.69	0.31%	FAIR	Y	35910-503	10/06/98
COMPUTER DELL	$1,599.00	0.17%	FAIR	Y	90377	10/16/98
COMPUTER DELL	$1,859.00	0.19%	FAIR	Y	90487	01/05/99
TOTAL	$59,568.69	6.17%				