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Exposure to Tetrachloroethylene-Contaminated Drinking Water and the Risk of Pregnancy Loss

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Abstract

There is little information on the impact of solvent-contaminated drinking water on pregnancy outcomes. This retrospective cohort study examined whether maternal exposure to tetrachloroethylene (PCE) - contaminated drinking water in the Cape Cod region of Massachusetts influenced the risk of clinically recognized pregnancy loss. The study identified exposed (n=959) and unexposed (1,087) women who completed a questionnaire on their residential and pregnancy histories, and confounding variables. Exposure was estimated using water distribution system modeling software. No meaningful associations were seen between PCE exposure level and the risk of clinically recognized pregnancy loss at the exposure levels experienced by the study population. Because PCE remains a common water contaminant, it is important to continue monitoring its impact on women and their pregnancies.

Keywords

Tetrachloroethylene; Perchloroethylene; Drinking Water Contamination; Pregnancy Loss; Spontaneous Abortion; Stillbirth

INTRODUCTION

From May 1968 through March 1980, many public water departments in the New England area installed vinyl-lined asbestos-cement (VL/AC) water distribution pipes to prevent taste and odor problems. The vinyl lining, which was comprised of a slurry of vinyl toluene resin (Piccotex™) dissolved in the solvent tetrachloroethylene (perchloroethylene, PCE), was painted onto the inner surface of the pipe during manufacturing. VL/AC pipes were shipped to the water departments for installation after drying for 48 hours (Demond 1982). Because PCE is volatile, it was assumed that most would evaporate by the time the pipe was in use. However, large quantities of PCE remained in the lining and subsequently leached into the public drinking water supplies.

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Approximately 660 miles of VL/AC pipes were installed in Massachusetts. A large proportion was installed in the Cape Cod region either to replace existing pipes or to extend the water distribution system as the population grew. When the pollution was discovered in 1980, affected areas had levels ranging from 1.5 to 80 μg/L in pipes along main streets with medium and high water flow and from 1,600 to 7,750 μg/L in pipes along dead end streets with low water flow (Demond 1982). Most areas with elevated PCE concentrations were subsequently flushed with large volumes of water or remediated by continuously bleeding the lines until levels fell below 40 ug/L, the Suggested Action Guide at the time. The maximum contaminant level is currently 5 μg/L. During this period, levels of other measured drinking water contaminants were low (Swartz et al. 2003).

While health concerns regarding PCE are based mainly on its carcinogenicity (IARC 1995; U.S. Dept of Health and Human Services 2005), there are also concerns regarding an adverse effect on reproduction. Many animal experiments suggest a harmful impact of prenatal exposure to PCE, and the closely related solvent trichloroethylene (TCE), on offspring viability in rats, chicks, and rabbits (Healy et al. 1982; Bross et al. 1983; Nelson et al. 1980; Narotsky and Kavlock 1995; Schwetz et al. 1975; Elovaara et al. 1979; Belilies et al. 1980).

Epidemiological studies of pregnancy loss among women with occupational exposure to dry cleaning solvents have also observed positive associations (e.g., Bosco et al. 1987; Kyyronen et al. 1989; Kolstad et al. 1990; Olsen et al. 1990; Lindbohm et al. 1990; Windham, et al. 1991; Doyle et al. 1997). Only a few studies with mixed results have examined women exposed to solvent-contaminated drinking water (Lagakos et al. 1986; Bove et al. 1995; Massachusetts Department of Public Health 1996).

We undertook a population-based retrospective cohort study to examine the influence of maternal exposure to PCE contaminated drinking water on a variety of pregnancy and developmental outcomes, including low birth weight, prematurity and learning disabilities (Aschengrau et al., 2008; Janulewicz et al., 2008). The current report focuses on the risk of pregnancy loss following PCE exposure, using the reproductive histories reported by women in the parent cohort study.

MATERIALS AND METHODS

Selection of Study Population

This study was approved by the Institutional Review Boards of the Massachusetts Department of Public Health and Boston University Medical Center, and by the 24A/B/11B Review Committee at the Massachusetts Department of Public Health. Women were eligible for the parent cohort study if they gave birth to a child (termed “index child”) from 1969 through 1983 and were living in one of eight Cape Cod towns with some VL/AC water distribution pipes at the time of the child’s birth. Eligible women were identified by cross-matching the maternal address on the birth certificate against water distribution system data gathered from water department records. The latter was stored in a Geographic Information System (GIS) that included the location, installation year, and diameter of all VL/AC pipes in the region.

Two groups of women were selected for the parent study: (1) women who were exposed to PCE-contaminated drinking water when the index child was born, and (2) women who were unexposed when the index child was born. A total of 1,492 women were initially designated as “exposed” because they were living at a residence at the time of the index child’s birth that was either adjacent to a VL/AC pipe or was adjacent to a pipe connected to a VL/AC pipe and the only possible water flow to their residence was through the VL/AC pipe. This

initial designation was based on visually inspecting maps of the pipe distribution network in the immediate vicinity of the maternal address on the birth certificate.

A comparison group of women initially designated as “unexposed” was randomly selected from the remaining resident women who gave birth during this period. “Unexposed” women were frequency matched to “exposed” women on the month and year of birth of the index child. A total of 1,704 women were selected for the “unexposed” comparison group. The initial exposure status of a woman was considered tentative until questionnaire data on private well use were reviewed and extensive exposure assessments, as described below, were conducted.

Follow-Up and Enrollment of Study Subjects

During 2002–2003, mothers were traced to find up-to-date addresses and telephone numbers. Letters were sent to all traced mothers (and fathers, if the mother was deceased) requesting that they complete a self-administered questionnaire. Two follow-up letters were sent to non-respondents, and individuals who did not respond to these letters were phoned. As described in Table 1, 8.4% of the selected population could not be located, 18.2% were located but never responded to any of our contact attempts, and 8.9% refused to participate. A small percentage of subjects (0.5%) were deceased or were ineligible because the birth certificate address was a temporary residence. Overall, 64.0% of the selected population and 69.9% of the successfully traced population returned the self-administered questionnaire. These percentages were similar for both “exposed” and “unexposed” subjects.

When we compared the demographic characteristics of participants and non-participants, we found that the race of non-participants (96.2% white) was nearly identical to that of the participants (96.2% white). However, non-participating women were younger (mean age 26.0 vs. 27.5 years), and less educated (11.3% did not graduate from high school vs. 3.6%) than participating women. These differences were present for both exposed and unexposed non-participants.

The self-administered questionnaire gathered information on maternal demographic characteristics; a complete history of all pregnancy outcomes, including prior losses; data on prenatal care, smoking, alcohol intake for each pregnancy; medical conditions such as diabetes and hypertension; occupational exposure to solvents; and use of solvent-based spot removers, and professional and self-service dry cleaning. In addition, information was collected on the family’s residences from 1969 to 1990, including the calendar years of residence, street address, and drinking water source for all Cape Cod residences. While we attempted to collect information on the mother’s water consumption and bathing habits at these residences, this information could not be recalled well enough to permit a meaningful analysis. Lastly, to evaluate the presence of recall bias, we gathered information on women’s knowledge of the PCE contamination episode, including whether or not they believed that their own drinking water may have been contaminated.

Following receipt of a completed questionnaire, we requested permission to review the prenatal and delivery records of index birth children. About 250 women agreed to release these records and records for 60 women were obtained. The remainder could not be located by the delivery hospital or obstetrician. The reproductive histories and related information in these medical records were compared to that reported by the women in the self-administered questionnaires. We also compared reproductive history data reported on the birth certificates with that on the questionnaires. The latter analyses were conducted among all index births in the study population.

Geocoding of Residential Addresses

All reported residences on Cape Cod were incorporated into a GIS by geocoding each address to a latitude and longitude using ArcGIS 8.1. We assigned each address to a parcel of land, whenever possible. All geocoding was conducted without knowledge of the exposure status or pregnancy history. Among the 5,324 reported addresses, 97.3% were successfully geocoded. The remainder could not be geocoded because of insufficient information. Our geocoding match rate was greater than or equal to that observed in recent epidemiological studies (e.g., McElroy et al. 2003; Gilboa et al. 2006).

PCE Exposure Assessment

Women received initial exposure designations based on a visual inspection of maps of the pipe distribution network in the immediate vicinity of the address listed on the index child's birth certificate. To determine the exposure status for each reported pregnancy, we used a leaching and transport model to estimate the mass of PCE that was delivered to each residence before and during the pregnancy. The model, which was developed by Webler and Brown for our prior epidemiological studies (Webler and Brown 1993; Aschengrau et al. 2003), estimates the amount of PCE entering the drinking water using the initial PCE loading in the pipe liner, the pipe's age, and the leaching rate of PCE from the liner into the drinking water. The pipe's initial stock of PCE is based on the diameter and length of the pipe and information from the pipe manufacturer on the application of the liner. The leaching rate of PCE from the liner was determined from experiments conducted by Demond (Demond 1982).

The algorithm also requires an estimate of water flow and direction, which are functions of the geometry of the distribution system and number of water users. In the current study, we estimated water flow and direction by incorporating the Webler and Brown algorithm into EPANET water distribution system modeling software. Developed by the U.S. Environmental Protection Agency, EPANET software has been used for exposure assessment of drinking water contaminants in several epidemiological studies (Rossman 1994; Aral et al. 1996; Gallagher et al. 1998; Maslia et al. 2000; Reif et al. 2003).

Using GIS maps of subject residences and a town's entire water distribution system, we created a diagram in EPANET depicting the water source locations; pipe length, diameter and composition; and nodes, the points along the pipe where water consumption occurs. Information on the locations, installation dates, and diameters of all VL/AC pipes was obtained from local water companies and the Massachusetts Department of Environmental Protection (DEP). The available information described the water system conditions around 1980, and so we chose this year as representative of the water flow during the entire study period.

We assigned each residence to the closest node on the distribution system. We assumed that land parcels represented water users and that all users on the network drew the same amount of water. These were reasonable assumptions because the study area was mainly comprised of residences. We also assumed that water sources did not change over the study period. The distribution systems in place by the 1960s and early 1970s remained largely unchanged until population growth required the addition of a few water sources in the late 1980s.

The EPANET software incorporated these data to simulate the instantaneous flow of water through thousands of pipe segments in each town's network and to estimate the mass of PCE in grams delivered to each node and all subjects' residences associated with the node. Annual exposure assessments were conducted from 1968, the earliest installation of AC/VL pipes, through 1990. The latter cut off was selected because of changes in population density and the water distribution systems during recent years.

We used the reproductive histories from the self-administered questionnaires to identify all clinically recognized pregnancy outcomes, including miscarriages, stillbirths, induced abortions, ectopic pregnancies, and live births. Eligible pregnancies for the current analyses were clinically recognized pregnancy losses (including miscarriages and stillbirths) and live births occurring up to December, 1990. As is typically done in retrospective studies of pregnancy outcomes (e.g., Whelan et al. 2007), induced abortions (n=327) and ectopic pregnancies (n=40) were excluded from the analysis. The 2,046 women who returned a study questionnaire contributed 5,567 eligible pregnancies: 659 pregnancy losses and 4,908 live births. Thus, 11.8% of eligible pregnancies resulted in a reported loss and 24.2% of women reported a prior loss at some point in their history. One hundred and fifty-six women contributed only one pregnancy while 674 contributed two pregnancies, and 1,061 contributed three or more. The number of losses per woman ranged from 0 to 6, and the number of live births ranged from 0 to 11. A woman could contribute both exposed and unexposed pregnancies.

We calculated three measures of a woman's PCE exposure: cumulative PCE exposure up to the month and year of the last menstrual period (LMP) of the pregnancy, peak exposure up to the LMP year of the pregnancy, and average monthly PCE exposure during the LMP year. The former two measures served as estimates of pre-pregnancy exposure while the latter estimated exposure around the time of conception. The first trimester was completed during the same year as the LMP for 85% of study pregnancies, and the Pearson correlation coefficient between annual exposure levels during the LMP and first trimester years was 0.96 ($p<0.0001$).

Cumulative exposure was estimated by summing the annual mass of PCE that entered each exposed residence from the move-in year or VL/AC pipe installation year through the month and year of the LMP. We were able to calculate only annual PCE exposures because only move-in and pipe installation *years* were known. Simple percentages were used to estimate the PCE exposure for a portion of a year. For example, if an exposed woman's LMP occurred in June of a particular year, we multiplied her annual PCE exposure during that year by $6/12^{th}$ or 0.50. Peak pre-pregnancy exposure was estimated from the highest annual mass of PCE that entered the residence up to the LMP year. Average monthly PCE exposure during the LMP year was estimated by dividing the annual exposure during the LMP year by twelve. The month and year of the LMP was estimated from questionnaire or birth certificate data. Pregnancies with inestimable LMPs were excluded from the analysis.

We estimated PCE exposure levels only for livebirths and losses associated with completely geocoded residential histories (94.2% of reported pregnancies). Three hundred and forty-four pregnancies were associated with inadequate residential histories, and so were excluded from the analysis. All pregnancies among women who reported using a private well for their drinking water supply at a Cape Cod address (20%) or who lived in a Cape Cod town without any VL/AC pipes were assumed to have no PCE exposure during that period. We considered these assumptions reasonable because, to the best of our knowledge, these water supplies were not contaminated with PCE in this geographic area and time period.

Statistical Analysis

The data analysis compared the occurrence of pregnancy losses among exposed and unexposed pregnancies. When cumulative exposure was examined, women who had any exposure up to the LMP were compared to those who were unexposed before the LMP, and when peak annual exposure before pregnancy was examined, any exposure before the LMP year was compared to no exposure before the LMP year. Similarly, when exposure during the LMP year was examined, women with any exposure during the LMP year were compared to those with no exposure during the LMP year. We used a locally weighted

regression smoother (LOESS) to examine the shape of the relationship between each exposure measure and the outcome (Hastie et al. 1990). These analyses did not identify any natural cut points, so we arbitrarily divided each exposure measure into quartiles. In addition, we dichotomized the average monthly exposure during the LMP year at the level corresponding to an average drinking water concentration of 40 ug/L, the Suggested Action Guide when the pollution was discovered in 1980.

Generalized estimating equation (GEE) analyses were conducted to account for non-independent outcomes arising from multiple pregnancies for same woman (Liang et al. 1986; Zeger et al. 1986). The logit link was used for the outcome, assuming equal correlation between birth outcomes from the same mother. Corresponding odds ratios measured the strength of the associations and 95% confidence intervals assessed their statistical stability.

Maternal age was included in all multivariate analyses. Additional covariates considered were either known risk factors for pregnancy loss, associated with PCE exposure, or non-drinking water sources of solvent exposure. These variables included year of pregnancy, paternal age and occupation, maternal race, educational level, number of prior live births, history of a prior induced abortion, history of prior losses (before any PCE exposure among exposed pregnancies and before a randomly assigned index year for unexposed pregnancies); behavioral characteristics during pregnancy including cigarette smoking, alcohol and caffeinated beverage consumption, and marijuana use; medical conditions including diabetes, thyroid disease, cervical incompetence, placental conditions, and a history of gynecologic infections; use of an intrauterine device or spermicides at conception; residence in Falmouth, the only study town with a chlorinated surface water supply (as a proxy for trihalomethane exposure during the LMP year); maternal occupational exposure to solvents, use of solvent-based spot removers and professional and self-service dry cleaning; and the proximity of any residences to dry cleaning establishments.

Covariates were included in the final multivariate models if they altered the maternal age-adjusted odds ratios by at least 5%. Four variables met this criterion: year of pregnancy, paternal age, maternal history of gynecologic infections, and number of prior livebirths.

Stratified analyses were also conducted to determine if there was effect measure modification by maternal age, a history of prior losses; year of pregnancy, medical or obstetrical conditions; cigarette smoking, and alcohol consumption during the first trimester, and residence in Falmouth. Analyses were also conducted according to the trimester of the loss (first vs. second and third) in order to assess whether PCE was associated with losses arising from chromosomal abnormalities, which mainly occur during the first trimester. Lastly, analyses compared the women's self-assessed exposures from the questionnaires with the independent EPANET assessment to determine if recall bias was likely.

RESULTS

A total of 1,891 women with 5,567 clinically recognized pregnancies were available for the final analysis. The frequency of pregnancy loss among eligible pregnancies was 11.8% and the frequency of one or more pregnancy losses among eligible women was 24.2%. Following the EPANET exposure assessment, there was 283 pregnancy losses and 2,112 livebirths with some exposure before the LMP and 376 pregnancy losses and 2,796 livebirths with no exposure before the LMP. In addition, there were 213 pregnancy losses and 1,743 livebirths with some exposure during the LMP year and 446 pregnancy losses and 3,165 livebirths with no exposure during the LMP year.

While we were able to validate only a small number of pregnancy outcomes using original prenatal and obstetric records, we found excellent agreement between the questionnaires and medical records. For example, 92% of clinically recognized miscarriages, and 100% of the livebirths noted in medical record were reported in the survey. There was also excellent agreement between the medical record and survey on gestational duration, birth weight, and prenatal cigarette smoking and multivitamin use. Furthermore, when we compared the questionnaire and birth certificate data from all index births (n=2490), we found good to excellent agreement on month and year of birth, mother's and father's age at the birth, birth weight, number of prior live births and number of prior pregnancy terminations (including spontaneous and induced abortions).

Many characteristics of exposed and unexposed subjects was similar (Table 2). Mothers in both groups were predominantly white, and comparable proportions had prior induced abortions, peri-conceptional contraceptive use, medical conditions and pregnancy complications, and exposure to non-drinking water sources of solvents. However, because of the timing and location of the VL/AC pipe installations, exposed losses and livebirths were more likely to occur in later calendar years and among residents of Falmouth, the only town with a treated surface water supply and 50 miles of VL/AC pipe. In addition, the average maternal and paternal age, maternal educational level, socioeconomic status (as measured by paternal occupation) and number of prior livebirths were higher among exposed pregnancies. In contrast, cigarette smoking, and alcohol consumption during the first trimester was less common among exposed pregnancies.

There was wide distribution of PCE exposure levels encompassing several orders of magnitude among the exposed pregnancies (Table 3). The median levels of cumulative exposure, maximum annual exposure, and average monthly exposure were 27, 16 and 0.55 grams, respectively. As previously described, the exposure measures were based on the mass of PCE delivered to a home in each calendar year. The annual mass of PCE entering a home was diluted in an estimated 90,000 gallons of water, the annual usage of average households in Massachusetts (Massachusetts Water Resources Authority 2003), and only a small portion of this water was directly consumed by the subjects. Using this annual estimate of household water use, we converted the PCE mass delivered to a home during pregnancy to average annual point concentrations and estimated that the PCE concentrations in the water entering the homes ranged from less than 1 ug/L to 5,197 ug/L. These concentrations are consistent with actual water sampling data from the time period (Demond 1982).

When we compared the women's self-assessed exposure status to that derived from the EPANET assessment, we found that only 15% of women considered exposed by the EPANET assessment thought that their drinking water was contaminated, whereas 28% of these women thought that their water was not contaminated and 57% were unsure. Similarly, we found that 37% of women considered unexposed by the EPANET assessment thought that their drinking water was not contaminated while 9% thought that their drinking water was contaminated and 53% were unsure.

The crude and multivariate adjusted odds ratios for pregnancy loss were quite similar across exposure categories (Table 4). For example, compared to women who were unexposed during the LMP year, the multivariate GEE odds ratios were 1.1, 0.7, 0.8 and 0.7 for women whose average monthly PCE exposure during the LMP year ranged from the lowest to highest exposure quartile. Similar results were seen when cumulative and peak PCE exposures were examined. In addition, the multivariate GEE odds ratio for pregnancy loss was not elevated (OR: 0.8, 95% CI: 0.6–1.1) among women whose average monthly exposure during the LMP year was greater than 1.136 grams, a cut point which corresponds

to an average drinking water concentration of 40 ug/L. The results were unchanged when the pregnancies were stratified according to year of pregnancy.

The exposed and unexposed losses had a similar distribution of gestational duration (Table 2). When the losses were stratified by trimester, we did not observe any increases in the risk of either early or late pregnancy losses according to any of the exposure measures (Table 5).

There was also no evidence of effect measure modification by maternal age, history of prior losses, medical conditions, alcoholic beverage and cigarette smoking during the first trimester, and residence in the town of Falmouth (data not shown).

DISCUSSION

The results of this study suggest that pre-natal PCE exposure, at the levels experienced by this population, does not increase the risk of clinically recognized pregnancy loss. As compared to unexposed pregnancies, the adjusted odds ratios for pregnancy loss were either at or below the null among women whose PCE exposure levels ranged from the lowest to highest quartile. Furthermore, no elevation in risk was observed among women whose average monthly exposure during the LMP year was greater 1.136 grams, a cutpoint which corresponds to an average drinking water concentration of 40 ug/L, the Suggested Action Guide when the PCE contamination was discovered.

A causal interpretation of these findings results is tempered by likely exposure misclassification. Because individual level exposure measurements were not available for the study period, we estimated historical PCE exposures using a leaching and transport model developed by Webler and Brown (Webler and Brown, 1993) that predicted the mass of PCE delivered to each residence. The model was applied to water distribution system conditions in 1980 assumed to be representative of the entire study period. Further misclassification arose from our inability to incorporate water consumption and bathing habits into the analysis because mothers had poor recall of this information.

On the other hand, results from two validation studies indicate good correlation between PCE concentrations in historical water samples and exposure estimates based on the original Webler-Brown flow algorithm (Spearman correlation coefficient=0.48, $p<0.0001$) (Spence et al. 2008), as well as exposure estimates based on the EPANET water distribution system modeling software (Spearman correlation coefficient=0.65, $P<0.001$) (Gallagher et al. unpublished manuscript). While these validation study results suggest the magnitude of exposure misclassification is relatively small, particularly given the quartile exposure categories used in the current analysis, it likely hampered our ability to detect a modest increase in the risk of pregnancy loss.

Another limitation arose from our use of self-reported pregnancy losses. While some under-reporting of clinically recognized losses was likely (11.8% of reported pregnancies ended in a loss and 24.2% of women had a history of a loss), results of our outcome validation study, albeit small in size, showed good reporting of pregnancy outcomes and related behaviors. Furthermore, the proportion of reported losses was stable over time and the breakdown of losses by trimester was as expected. Lastly, our analyses of index births found good agreement between the number of pregnancy terminations (induced and spontaneous) reported by the women and on the birth certificate.

Another limitation of the study arose from using birth certificates to identify women for the parent study. While parity was controlled in the present analysis, these results may not be generalizable to women who never achieve a livebirth, an estimated 12% of women in the United States (Chandra et al., 2005).

The present study has numerous strengths, including a relatively large number of pregnancy losses, a wide range and irregular pattern of exposure, and information on many confounding variables. In addition, confounding by unmeasured drinking water contaminants was unlikely. Trihalomethane levels in this region were low because only one surface water source was treated. Furthermore, the results were unchanged when we controlled for residence in Falmouth, the only study town with a chlorinated surface water supply. While non-participating mothers were younger and less educated than participating mothers, these differences were present for both exposed and unexposed non-participants, and so it is unlikely that selection bias influenced the current results. Recall bias was also unlikely because the PCE exposure assessments were conducted blindly with respect to the pregnancy outcome information. Furthermore, there was poor agreement between a woman's self-assessed exposure and the exposure status derived independently for the study. In fact, most women were unsure if their own drinking water had been contaminated with PCE.

Several animal experiments suggest that PCE and TCE cause species- and dose-specific increases in embryotoxicity. Increased rates of resorbed implants and fetuses have been observed in many studies of pregnant rats exposed to low, moderate and high doses of these chemicals (e.g., 100 to 1000 ppm for inhalation doses) (Healy et al. 1978; Smith et al. 1989; Schwetz et al. 1975; Narotsky and Kavlock 1995; Tinston 1995). The proportion of dead embryos also increased in a dose-dependent fashion among fertilized Leghorn chick eggs whose air space was injected with 5–100 umol PCE and TCE (Elovaara et al. 1979). Lastly, increased resorptions have been seen among rabbits with inhalation exposures of 500 ppm PCE and TCE. In contrast, no evidence of embryotoxicity has been observed among mice exposed to low and moderate doses (i.e., 100–500 ppm) (Beliles et al. 1980; Hardin et al. 1981; Schwetz et al. 1975).

Many epidemiological studies also have found a positive association between maternal occupational exposure to solvent mixtures and the risk of pregnancy loss (e.g., Khattak et al. 1999); however, results are often difficult to interpret because many types of solvents and jobs were included in the exposed group. Nevertheless, numerous studies with more specific exposure definitions, such as dry cleaning work or PCE exposure, have measured an increased relative risk of pregnancy loss (e.g., Bosco et al. 1987; Kyyronen et al. 1989; Kolstad et al. 1990; Olsen et al. 1990; Lindbohm et al. 1990; Windham, et al. 1991; Doyle et al. 1997). The reported relative risks range from about 1.4 to 4.0. In contrast, a few occupational studies did not find any increases in the risk of pregnancy loss among laundry and dry cleaning workers (e.g, Ahlborg 1990; McDonald et al. 1987), but the broad exposure categories likely biased these results toward the null.

Studies by Windham et al. (1991) and Doyle et al. (1997) were among the largest of the occupational studies with positive associations, with 628 and 422 pregnancy losses, respectively. The case-control study by Windham et al. found a 3.4-fold increased risk of spontaneous abortion (95% CI: 1.0–12.0) among pregnant women with occupational exposure to PCE and/or TCE, while the retrospective cohort study by Doyle et al. found a 1.6-fold increased risk (95% CI: 1.1–2.7) among women employed as dry cleaning operators with a high likelihood of PCE exposure.

A likely reason for the discrepancy between our null results and the positive associations seen in these occupational studies is the difference in exposure levels. Allowable occupational exposure levels for PCE are relatively high (ATSDR 1997), especially in comparison to the environmental exposures experienced by most of our study population. In addition, occupational studies comparing working and nonworking women, such as those by Bosco et al. (1987) and Doyle et al. (1997), may have an upward bias because women whose

pregnancy history is comprised only of adverse outcomes such as pregnancy losses are more likely to remain in the work force, while those who have had live born children are more likely to drop out (Joffe 1985). The study by Windham et al. (1991) specifically limited the analyses to working women to avoid this problem.

Furthermore, the increased risks among women with occupational exposures may not be generalizable to women in the general population because solvent-exposed women come mainly from low socioeconomic strata. In addition, women who either cannot find work or do not have a monetary incentive to work are not represented in the occupational studies.

Prior population-based studies of solvent contaminated drinking water are more analogous to the current investigation. Only three prior drinking water studies have examined PCE and TCE contamination in relation to pregnancy loss, and two of the three studies have null results. A cross-sectional study from New Jersey found no increase in the risk of fetal death in relation to PCE or TCE exposure using town-level exposure data provided by the water companies and vital records data on fetal deaths occurring at > 20 weeks' gestation (Bove et al. 1995; Bove et al. 2002).

Another cross-sectional study in Woburn, Massachusetts found no elevation in the risk of spontaneous abortion in relation to the fraction of residential water obtained from two contaminated wells during the year the pregnancy ended (Lagakos et al. 1986). The two wells, known as Wells G and H, were contaminated with TCE (267 ug/L), PCE (21 ug/L), and several other chemicals. Woburn Study investigators obtained data on spontaneous abortions from subject interviews, and estimated prenatal exposure to the contaminated wells using a water distribution model. In contrast, a follow-up study in Woburn found a 1.8-fold increased risk of fetal death among women with any exposure during pregnancy (95% CI: 0.4–6.6), and a 2.6-fold increased risk (95% CI: 0.7–8.9) among women with high exposure during pregnancy (Massachusetts Department of Public Health 1996; Bove et al. 2002). In the follow-up study, reports of fetal deaths were obtained from the Massachusetts Registry of Vital Records, and included only deaths at >= 20 weeks' gestation or in fetuses weighing >= 350 grams. In addition, a more sensitive model of the water distribution system estimated prenatal exposures.

Taken together, the results of the present and prior studies do not provide strong evidence of an increased risk of clinically recognized pregnancy loss in relation to PCE exposure from drinking water. However, weaknesses in these studies, including the present one, may have made it difficult to observe a modestly increased risk. Furthermore, our results are not generalizable to women with unrecognized pregnancy loss or to women who have never achieved a livebirth. Because PCE remains a commercially ubiquitous solvent and common contaminant of ground and drinking water supplies (Moran et al. 2007; ATSDR 1997), it is important to understand its effect on women and their pregnancies.

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Table 1

Selection and Enrollment According to Woman's PCE Exposure Status, Cape Cod, Massachusetts

	Initial Exposure Status[a]		
	Exposed	**Unexposed**	**Total**
Selected	1,492	1,704	3,196
Excluded During Enrollment			
Never located	132	136	268
No response	245	336	581
Ineligible or Deceased	7	8	15
Refusal	149	137	286
Returned Questionnaire	959	1,087	2,046
% of selected	64.3%	63.8%	64.0%
% of located	70.5%	69.3%	69.9%

[a]The exposure status of the women's pregnancy losses and livebirths was later assessed. See text for details.

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Table 2

Distribution of Selected Characteristics of Exposed and Unexposed Pregnancies[a]

	Exposed				Unexposed			
	Losses		Livebirths		Losses		Livebirths	
	n	%	n	%	n	%	n	%
Characteristic								
Year of pregnancy								
Before 1968	0	0.0	0	0.0	55	12.3	347	11.0
1968–1974	25	11.7	264	15.1	129	28.9	851	26.9
1975–1980	93	43.7	749	43.0	137	30.7	1097	34.7
After 1980	95	44.6	730	41.9	125	28.0	870	27.5
Gestational duration								
Up to 13 weeks	170	79.8	0	0.0	350	78.5	0	0.0
14–26 weeks	24	11.3	9	0.5	79	17.7	12	0.4
> 26 weeks	19	8.9	1734	99.5	17	3.8	3153	99.6
Maternal age (n, mean)	211	29.0	1730	27.7	442	26.7	3147	26.0
Paternal age (n, mean)	202	31.2	1729	30.9	417	29.4	3109	29.0
Race								
White	197	92.5	1662	95.4	419	93.9	3021	95.5
Non-White	14	6.6	77	4.4	22	4.9	132	4.2
Missing	2	0.9	4	0.2	5	1.1	12	0.4
Educational level								
< High school	7	3.3	27	1.5	6	1.3	70	2.2
High school graduate	24	11.3	324	18.6	85	19.1	649	20.5
Some college	71	33.3	602	34.5	164	36.8	1091	34.5
College graduate	109	51.2	785	45.0	188	42.2	1348	42.6
Missing	2	0.9	5	0.3	3	0.7	7	0.2
Paternal occupation								
White collar	114	53.5	888	50.9	207	46.4	1457	46.0
Blue collar	63	29.6	566	32.5	141	31.6	1064	33.6
Other	36	16.9	255	14.6	90	20.2	602	19.0
Missing	0	0.0	34	2.0	8	1.8	42	1.3

	Exposed				Unexposed			
	Losses		Livebirths		Losses		Livebirths	
	n	%	n	%	n	%	n	%
Number of prior livebirths								
0	54	25.4	534	30.6	150	33.6	1354	42.8
1	81	38.0	674	38.7	175	39.2	1012	32.0
2+	74	34.7	534	30.6	121	27.1	796	25.2
Missing	4	1.9	1	0.1	0	0.0	3	0.1
Prior pregnancy losses before PCE exposure or index year[b]								
Yes	34	16.0	147	8.4	94	21.1	254	8.0
No	177	83.1	1595	91.5	352	78.9	2908	91.9
Missing	2	0.9	1	0.1	0	0.0	3	0.1
Cigarette smoking during first trimester								
Some	48	22.5	430	24.7	136	30.5	953	30.1
None	164	77.0	1306	74.9	308	69.1	2183	69.0
Missing	1	0.5	7	0.4	2	0.4	29	0.9
Alcohol consumption during first trimester								
Some	68	31.9	639	36.7	178	40.0	1182	37.3
None	142	66.7	1093	62.7	265	59.4	1949	61.6
Missing	3	1.4	11	0.6	3	0.7	34	1.1
Marijuana use during pregnancy								
Yes	8	3.8	57	3.3	14	3.1	128	4.0
No	201	94.4	1665	95.5	429	96.2	2997	94.7
Missing	4	1.9	21	1.2	3	0.7	40	1.3
Cervical Incompetence	7	3.3	34	2.0	16	3.6	61	1.9
Occupational exposure to solvents								
Yes, before or during pregnancy	29	13.6	186	10.7	63	14.1	284	9.0
Yes, unknown when 1	0.5	26	1.5	9	2.0	46	1.5	
No	178	83.6	1503	86.2	368	82.5	2784	88.0
Missing	5	2.3	28	1.6	6	1.3	51	1.6
Use of solvent-based spot removers								
Yes	148	69.5	1127	64.7	313	70.2	2060	65.1

	Exposed				Unexposed			
	Losses		Livebirths		Losses		Livebirths	
	n	%	n	%	n	%	n	%
No	60	8.2	581	33.3	127	28.5	1026	32.4
Missing	5	2.3	35	2.0	6	1.3	79	2.5
Use of professional dry cleaning								
Yes	187	87.8	1495	85.8	377	84.5	2703	85.4
No	13	6.1	188	10.8	41	9.2	312	9.9
Missing	13	6.1	60	3.4	28	6.3	150	4.7
Use of self-service dry cleaning								
Yes	32	15.0	233	13.4	78	17.5	526	16.6
No	174	81.7	1456	83.5	361	80.9	2549	80.5
Missing	7	3.3	54	3.1	7	1.6	90	2.8
Surface water supply during LMP year	71	33.3	601	34.5	22	4.9	166	5.2

[a] Exposure status during LMP year of each pregnancy

[b] Prior losses before exposure for PCE exposed pregnancies or a comparable index year for unexposed pregnancies

Table 3

Distributions of Cumulative Exposure (g) up to LMP Month and Year, Maximum Annual Exposure (g) Before LMP Year, and Average Monthly Exposure (g) During LMP Year Among PCE Exposed Pregnancies

	Cumulative Exposure Up to LMP Month and Year	Maximum Annual Exposure Before LMP Year	Average Monthly Exposure During LMP Year
n	2,395[a]	2,047[a]	1,956[a]
Minimum	2.8E-04	1.2E-03	7.5E-05
10th Percentile	1	10.0E-01	2.3E-02
25th Percentile	6	4	1.2E-01
Median	27	16	5.5E-01
75th Percentile	113	55	2
90th Percentile	334	145	6
Maximum	4,019	1,698	132

[a] 439 subjects were exposed only before the LMP year, 348 subjects were exposed only during the LMP year, and 1,608 subjects were exposed both before and during the LMP year. Thus, 2,395 subjects (439 +1608 + 439 +348) contributed to the measure of cumulative exposure up to the LMP month and year, 2,047 subjects (1608 + 439) contributed to the maximum exposure before the LMP year, and 1,956 subjects (1608 + 348) contributed to the average monthly exposure during the LMP year.

Table 4

Frequencies, Odds Ratios and 95% Confidence Intervals for Pregnancy Loss According to PCE Exposure

	Number of Losses	Number of Livebirths	Crude Odds Ratio (95% CI)	Multivariate[a] GEE Odds Ratio (95% CI)
Cumulative PCE Exposure up to LMP (g)				
>= 75th pctile	70	529	1.0 (0.8–1.3)	0.9 (0.7–1.3)
50th – < 75th pctile	69	530	1.0 (0.7–1.3)	0.8 (0.6–1.2)
25th – < 50th pctile	68	531	1.0 (0.7–1.3)	0.9 (0.6–1.3)
>0 – < 25th pctile	76	522	1.1 (0.8–1.4)	1.1 (0.8–1.5)
0 (Referent)	376	2796	1.0 (----)	1.0 (----)
Maximum Annual PCE Before LMP Year (g)				
>= 75th pctile	63	449	1.1 (0.8–1.4)	1.1 (0.8–1.5)
50th – < 75th pctile	67	517	1.2 (0.9–1.5)	1.1 (0.8–1.7)
25th – < 50th pctile	53	507	0.9 (0.7–1.2)	0.8 (0.5–1.1)
>0 – < 25th pctile	74	511	1.3 (1.0–1.7)	1.4 (1.0–1.9)
0 (Referent)	402	3118	1.0 (----)	1.0 (----)
Average Monthly PCE Exposure During LMP Year (g)				
>= 75th pctile	46	443	0.7 (0.5–1.0)	0.7 (0.5–1.0)
50th – < 75th pctile	48	441	0.8 (0.6–1.1)	0.8 (0.6–1.2)
25th – < 50th pctile	53	436	0.9 (0.6–1.2)	0.7 (0.5–1.1)
>0 – < 25th pctile	66	423	1.1 (0.8–1.5)	1.1 (0.8–1.6)
0 (Referent)	446	3165	1.0 (----)	1.0 (----)

[a] Controlled for maternal age, paternal age, maternal history of gynecologic infections, number of prior livebirths, and year of pregnancy

Table 5

Frequencies, Odds Ratios and 95% Confidence Intervals for First and Second/Third Trimester Pregnancy Loss According to PCE Exposure

	Number of Losses	Number of Livebirths	Crude Odds Ratio (95% CI)	Multivariate[a] GEE Odds Ratio (95% CI)
First Trimester Losses				
Cumulative PCE Exposure up to LMP (g)				
>= 75th pctile	56	529	1.0 (0.7–1.3)	1.0 (0.7–1.4)
50th – < 75th pctile	51	530	0.9 (0.6–1.2)	0.8 (0.6–1.3)
25th – < 50th pctile	48	531	0.8 (0.6–1.2)	0.8 (0.5–1.2)
>0 – < 25th pctile	66	522	1.2 (0.9–1.6)	1.2 (0.8–1.7)
0 (Referent)	299	2796	1.0 (----)	1.0 (----)
Maximum Annual PCE Before LMP Year (g)				
>= 75th pctile	50	449	1.1 (0.8–1.5)	1.1 (0.8–1.6)
50th – < 75th pctile	54	450	1.2 (0.9–1.6)	1.2 (0.9–1.8)
25th – < 50th pctile	34	454	0.7 (0.5–1.1)	0.6 (0.4–1.0)
>0 – < 25th pctile	63	437	1.4 (1.0–1.9)	1.6 (1.1–2.2)
0 (Referent)	319	3118	1.0 (----)	1.0 (----)
Average Monthly PCE Exposure During LMP Year (g)				
>= 75th pctile	38	443	0.8 (0.5–1.1)	0.7 (0.5–1.1)
50th – < 75th pctile	34	441	0.7 (0.5–1.0)	0.8 (0.5–1.2)
25th – < 50th pctile	41	436	0.9 (0.6–1.2)	0.8 (0.5–1.2)
>0 – <25th pctile	57	423	1.2 (0.9–1.6)	1.3 (0.9–1.9)
0 (Referent)	350	3165	1.0 (----)	1.0 (----)
Second/Third Trimester Losses				
Cumulative PCE Exposure up to LMP (g)				
>= 75th pctile	14	529	1.0 (0.5–1.7)	0.8 (0.4–1.7)
50th – < 75th pctile	18	530	1.2 (0.7–2.1)	0.8 (0.4–1.7)
25th – < 50th pctile	20	531	1.4 (0.8–2.3)	1.3 (0.7–2.2)
>0 – < 25th pctile	10	522	0.7 (0.4–1.4)	0.7 (0.4–1.5)
0 (Referent)	77	2796	1.0 (----)	1.0 (----)
Maximum Annual PCE Before LMP Year (g)				
>= 75th pctile	13	449	1.1 (0.6–2.0)	1.0 (0.5–2.1)
50th – < 75th pctile	13	450	1.1 (0.6–2.0)	0.9 (0.4–1.9)
25th – < 50th pctile	19	454	1.6 (0.9–2.6)	1.3 (0.7–2.3)
>0 – < 25th pctile	11	437	0.9 (0.5–1.8)	1.0 (0.5–1.9)
0 (Referent)	83	3118	1.0 (----)	1.0 (----)
Average Monthly PCE Exposure During LMP Year (g)				
>= 75th pctile	8	443	0.6 (0.3–1.2)	0.6 (0.2–1.3)
50th – < 75th pctile	14	441	1.0 (0.6–1.8)	1.0 (0.5–1.9)
25th – < 50th pctile	12	436	0.9 (0.5–1.7)	0.6 (0.3–1.5)
>0 – < 25th pctile	9	423	0.7 (0.4–1.4)	0.7 (0.3–1.4)
0 (Referent)	96	3165	1.0 (----)	1.0 (----)

[a] Controlled for maternal age, paternal age, maternal history of gynecologic infections, number of prior livebirths, and year of pregnancy