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Reproductive and developmental health effects of prenatal exposure to tetrachloroethylene-contaminated drinking water

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Abstract

Tetrachloroethylene (PCE) is a common contaminant in both occupational and community settings. High exposure levels in the workplace have been shown to have adverse impacts on reproduction and development but few epidemiological studies have examined these effects at the lower levels commonly seen in community settings. We were presented with a unique opportunity to examine the reproductive and developmental effects of prenatal exposure to PCE-contaminated drinking water resulting from the installation of vinyl-lined water pipes in Massachusetts and Rhode Island from the late 1960s through 1980. This review describes the methods and findings of two community-based epidemiological studies, places their results in the context of the existing literature, and describes the strengths and challenges of conducting epidemiological research on a historical pollution episode. Our studies found that prenatal exposure to PCE-contaminated drinking water is associated with delayed time-to-pregnancy, and increased risks of placental

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Conflicts of interest

There are no conflicts to declare.

abruption, stillbirths stemming from placental dysfunction, and certain birth defects. No associations were observed with pregnancy loss, birth weight, and gestational duration. Important strengths of this research included the availability of historical data on the affected water systems, a relatively high exposure prevalence and wide range of exposure levels, and little opportunity for recall bias and confounding. Challenges arose mainly from the retrospective nature of the exposure assessments. This research highlights the importance of considering pregnant women and their developing fetuses when monitoring, regulating, and remediating drinking water contaminants.

Introduction

Tetrachloroethylene (also called perchloroethylene or PCE) is a solvent commonly used in dry cleaning, textile processing and metal degreasing.[1] Because most of its use occurs in small workplaces with poor waste management and disposal practices, PCE is a ubiquitous contaminant of ground and surface water supplies in the United States (U.S.).[1–3] Thus, it is not surprising that PCE has been detected in 77% of blood samples from a general population sample.[4]

While improper waste management and disposal is the typical manner by which PCE contaminates drinking water, an unusual scenario resulted in widespread contamination of public drinking water supplies in Massachusetts and Rhode Island from the late 1960s through the 1980s. Water pipes produced during this period contained a vinyl liner (VL) intended to eliminate taste and odor problems associated with asbestos-cement (AC) drinking water mains. The liner was applied by spraying a slurry of vinyl resin (Piccotex™, Johns-Manville Corporation, Denver, CO) dissolved in PCE. Because PCE is volatile it was assumed it would evaporate during the drying process.[5] However, water samples taken in 1980 revealed that substantial amounts of PCE remained in the liner and were leaching into public drinking water supplies.[6]

A survey of local water departments found approximately 750 miles of VL/AC pipes in nearly 100 communities in Massachusetts and Rhode Island.[7] The largest portion was installed in the Cape Cod region of Massachusetts which had undergone substantial residential development during this time. Like the irregular pattern of clean and polluted water found in John Snow's cholera investigation in 1854 London,[8] homes in the same Rhode Island and Massachusetts neighborhoods might have had very different PCE levels because of the irregular pattern of VL/AC pipes installation[9] (Fig. 1). PCE levels in water samples from affected pipes on Cape Cod ranged from 1.5 to 7750 μg L^{-1}, depending on the rate of water flow.[6] Levels of other measured drinking water contaminants were low during this time.[10]

Pipe locations with elevated PCE levels were subsequently flushed with large volumes of water or remediated by continuously bleeding the lines until the levels fell below 40 μg L^{-1}, the level that was considered "safe" in 1980.[6] This is eight times the current maximum contaminant level of 5 μg L^{-1} in the two states.[11,12]

A few years after the PCE contamination was discovered, the Massachusetts Department of Public Health reported elevations in cancer incidence and mortality in the Cape Cod region.[13] In 1988, In response to concerns about the possible relationship between the elevated cancer rates and pollution in the region, we undertook a case-control study to evaluate the carcinogenic potential of population exposure to air and water pollution, including PCE-contaminated drinking water.[14,15]

Several years after completing the cancer case-control studies, we initiated a retrospective birth cohort study ("Cape Cod Health Study") to examine a wider array of possible health consequences of PCE exposure, especially during the prenatal period. These included reproductive and developmental outcomes such as delayed time to pregnancy,[16] ischemic placental disease,[17] declines in birth weight and gestational duration,[18] pregnancy loss,[19] and congenital anomalies.[20] A case-control study ("Boston University (BU) Children's Health Study") was subsequently conducted in Massachusetts and Rhode Island to follow-up suggestive associations for congenital anomalies and stillbirths observed in the retrospective cohort study.[21,22] While animal experiments[23–26] and occupational studies among humans[27–29] suggested adverse impacts on reproduction, few epidemiological studies had examined reproductive and developmental effects at lower levels seen in community settings. The purpose of this review is to describe the methods and findings of our research, place the results in the context of the existing literature, and discuss the strengths and challenges of conducting research on a historical pollution episode in a community setting.

Cape Cod Health Study methods

The Cape Cod Health Study was a population-based retrospective cohort study was conducted from 2000 through 2005 with funding from the National Institute of Environmental Health Sciences (NIEHS) Superfund Research Program and the approval of the Institutional Review Boards of Boston University Medical Cancer and the Massachusetts Department of Public Health.

Identification of subjects

Mothers were eligible for the study if they gave birth to a child (termed "index child") between 1969 and 1983 while they were living in one of eight Cape Cod towns with some VL/AC water pipes.[18] Even though the installation of VL/AC pipes ceased in 1980, considerable exposure persisted for several years there-after.[5–7] Hence, the enrollment period included births through 1983. Mothers were initially identified as exposed ($N = 1910$) by cross-matching their addresses on birth certificates with information from local water companies on the locations and installation years of the VL/AC pipes. For comparison, unexposed women ($N = 1928$) were randomly selected from the remaining mothers and frequency matched to exposed women on month and year of birth. For practical reasons, the initial exposure assessments were based on visual inspection of pipe distribution maps in the vicinity of the maternal address on the birth certificate and were considered preliminary until more extensive assessments, as described below, were completed.

Birth certificates of index children were reviewed to obtain parents' and children's names; parents' age and educational level; maternal address at delivery and date of last menstrual

period; and the children's birth weight and gestational age. These data were obtained by interviewing mothers and reviewing medical records shortly after delivery.

Follow-up and data collection

Follow-up and enrollment of mothers occurred during 2002–2003.[18] Women were traced to find current addresses and telephone numbers. Letters were sent to all successfully traced women describing the general purpose of the study and requesting that they complete a self-administered questionnaire. Of the mothers who were selected for study, 8% could not be located, 18% were located but never responded to numerous contact attempts, 9% refused to participate, and 0.5% were ineligible or deceased, leaving 2125 (70.5% of those located) who returned the study questionnaire. Characteristics of participants and non-participants were similar, mitigating concerns of selection bias due to non-response.[18]

Using a self-administered questionnaire we gathered information on maternal demographic characteristics; water consumption and bathing habits; medical, lifestyle and occupational histories; and a detailed reproductive history, including time-to-pregnancy for planned pregnancies, pregnancy outcome, gestational duration, birth weight, congenital anomalies, and obstetrical complications.[18] Information was also collected on the family residences during the study period, including the calendar years of residence, street address and drinking water source (*i.e.* public or private) for all Cape Cod residences. Lastly, to evaluate the presence of recall bias, information was gathered on the mother's knowledge of the PCE contamination, including whether she believed her own drinking water was contaminated.

Geocoding and PCE exposure assessment

Approximately 97% of reported residential addresses on Cape Cod were geocoded to a latitude and longitude using ArcGIS 8.1 (ESRI, Redlands, CA) by a team member who was blinded to the exposure status and reproductive outcomes of the participant.[18] The remaining 3% could not be geocoded due to insufficient residential information. An initial exposure status was provisionally assigned to each woman by examining maps of the pipe network surrounding the birth residence and a leaching and transport model was then used to determine each woman's final exposure designation based on the estimated annual mass of PCE delivered to each residence.[18]

The leaching component of the model (developed for our cancer studies[14,15] by Webler and Brown) approximates the amount of PCE entering the drinking water by using the starting quantity of PCE in the liner, the age of the pipe, and the leaching rate of PCE from the liner into the water.[30] The pipe's initial stock of PCE was estimated using the pipe's diameter and length. The leaching rate was derived from laboratory experiments suggesting that decay followed a simple exponential process with rate constant of 2.25 years.[5]

The subsequent transport of PCE through the distribution system was modeled by incorporating Webler and Brown's leaching algorithm into the open source code of EPANET, water distribution software developed by the U.S. EPA.[30,31] This software has been used in several epidemiological studies evaluating health effects of drinking water contaminants.[32,33]

A geographic information system (GIS) platform facilitated the exposure assessment process by integrating the residential locations with the water system characteristics enabling the leaching and transport model to estimate the annual mass of PCE distributed to each woman's residence.[18] This involved creating a schematic that depicted the water source locations, pipe characteristics, points of water consumption, and residences. The EPANET software incorporated these data to simulate the flow of water through the pipe network and to estimate the annual mass of PCE in grams delivered to each subject's residence.

A validation study was also conducted to determine the accuracy of our modeled PCE exposure estimates. The study compared our modeled estimates with PCE concentrations from 75 water samples taken by state and town officials in 1980 before any remediation efforts were undertaken.[34] The study found good correlation between our modeled estimates and PCE concentrations in the historical water samples (Spearman correlation coefficient (ρ) = 0.65, $p < 0.00010$).

Various measures of prenatal PCE exposure were examined in relation to each reproductive outcome. For example, cumulative exposure before pregnancy and average monthly exposure around the time of conception were examined in relation to pregnancy loss, birthweight, and gestational duration.[18,19] Cumulative exposure before pregnancy 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 (whichever came later) through the month and year of the last menstrual period (LMP). We were able to calculate only annual PCE exposures because we knew only the move-in and pipe installation years. We used simple percentages to estimate PCE exposure for a portion of a year. Average monthly exposure around the time of conception was estimated by dividing the annual exposure during the LMP year by 12. Poor recall of bottle water use and bathing practices during pregnancy precluded incorporating these behaviors into the exposure assessments.[18] However, these factors were shown to have little impact on the exposure distribution in our prior cancer study.[35]

Data analysis

The analysis first compared the occurrence of each reproductive and developmental outcome among mothers with any prenatal PCE exposure to unexposed mothers.[18] Next, PCE exposure levels were examined to investigate possible dose-response relationships. The number of exposure levels depended on the particular health outcome. For example, four exposure levels were used for relatively common outcomes such as pregnancy loss but only two or three were used for rarer outcomes such as ischemic placental disease. Odds ratios (OR) or risk ratios (RR) were used to estimate the strength of the association between PCE exposure and dichotomous outcomes; mean differences were used to assess associations for continuous outcomes. Ninety-five percent confidence intervals (95% CI) were used to measure the precision of these associations. Generalized estimating equation analyses were conducted to account for non-independent outcomes arising from several children born to the same women.[36,37] Sixteen percent of women had two or more births during the study period. Confounding variables considered in adjusted analyses included demographic

characteristics, known risk factors for the reproductive outcomes, and non-drinking water sources of solvent exposure.

Cape Cod Health Study results and discussion

Participant characteristics

Cape Cod Health Study participants were predominantly white, college-educated, and, on average, 27 years old when the index child was born (Table 1).[18] Demographic and behavioral characteristics of exposed and unexposed mothers were quite similar indicating little or no confounding. The study population had a wide distribution of prenatal PCE levels encompassing several orders of magnitude (Table 2).[18]

Results and discussion for time-to-pregnancy[16]

Our study found little evidence for long-term, cumulative adverse effects of PCE exposure on time-to-pregnancy (TP). Any cumulative PCE exposure before pregnancy was associated with a 15% reduced risk of prolonged time to pregnancy (RR for greater than 12 months = 0.85, 95% CI: 0.70–1.03). However, high exposure levels around the time of pregnancy attempt were associated with longer TTP. Women with the highest average monthly PCE exposure around the time of pregnancy attempt (≥2.5 grams) had a 36% increased risk of time-to-pregnancy greater than 12 months (RR = 1.36, 95% CI: 1.06–1.76). Ancillary analyses did not find an increased risk of polycystic ovary syndrome or other benign gynecological conditions among PCE exposed women, suggesting that these conditions were not the reasons for the delayed time-to-pregnancy.[38]

While our finding of an increased risk of TTP greater than 12 months for the highest average monthly exposure (≥2.5 grams) may be underestimated due to the exclusion of women who never achieved a livebirth from the study population, this result is consistent with occupational studies examining TTP among female and male dry cleaning workers, where PCE is the predominant solvent used. Danish women exposed to dry-cleaning chemicals had a 60% higher risk of infertility compared with unexposed women.[39] Likewise, a study of Finnish women found that dry cleaning work was associated with reduced fecundability (fecundability ratio (FR), the probability of pregnancy in exposed compared with unexposed women = 0.44).[40] A California study also found that the wives of dry cleaning workers had lower fecundability (FR = 0.54) than the wives of laundry workers.[41] Taken together, the current literature suggests that adverse effects on TTP are unlikely to be experienced by the general population at levels below the current EPA regulations but that higher exposure levels in occupational and community settings could lengthen TTP.

Results and discussion for birth weight and gestational duration[18]

Our study did not observe meaningful associations between PCE exposure and birth weight or gestational duration. Compared with children whose mothers were unexposed, adjusted mean differences in birth weight were +20.9, +6.2, +30.1 and +15.2 grams for children whose mothers' average monthly exposure during the LMP year ranged from the lowest to highest quartile (see Table 2 for quartile values). In other words, children of exposed mothers had, on average, slightly higher birth weights than children of unexposed mothers.

Similarly, compared to unexposed children, adjusted mean differences in gestational age were −0.2, +0.1, −0.1, and −0.2 weeks across increasing quartiles of mothers' average monthly exposure during the LMP year.

Animal experiments suggest that an adverse effect on birth weight occurs in several species after prenatal exposure to PCE and the closely related solvent trichloroethylene (TCE).[24,25,42,43] Epidemiological studies of women exposed occupationally to solvents including dry cleaning and degreasing agents have inconsistent results regarding an adverse effect on birth weight and gestational duration. Eight studies found null associations,[28,44–50] while four studies observed increases in the risk of low birth weight or declines in mean birth weight.[51–54] Likewise, three previous occupational studies found null associations between prenatal solvent exposure and gestational duration,[47,51,54] while four found positive associations for the risk of preterm delivery.[46,52,53,55]

Two community-based studies of PCE and TCE drinking water contamination have null findings for gestational duration[56,57] while another found a modest association (OR: 1.3, 95% CI: 1.0–1.6) between preterm birth and the highest PCE exposure category.[58] While three prior community-based studies observed no meaningful increases in the risk of term low birth weight (defined as <2500 grams),[56,58,59] two studies observed increases in the risk of very low birth weight (defined as <1500 grams).[56,59]

Taken together, the current literature suggests that high levels of prenatal exposure in occupational settings may have adverse effects on birth weight and gestational duration but there is little evidence for an adverse impact of lower exposure levels through drinking water.

Results and discussion for pregnancy loss[19]

Our study found no meaningful associations between prenatal PCE exposure levels and the risk of pregnancy loss at any time during pregnancy. Compared to pregnancies unexposed around the time of conception, the adjusted odds ratios for pregnancy loss were either at or below the null for all PCE exposure levels (adjusted ORs were 1.1, 0.7, 0.8 and 0.7 from the lowest to highest exposure quartile).

Our null findings stand in contrast to animal studies showing embryotoxicity[61–63] and several occupational studies that found increased risks of pregnancy loss among female workers exposed to PCE and other solvents.[27–29,45,63–65] The small literature on drinking water exposures have divergent results. A prior cross-sectional study from New Jersey found no increase in the risk of fetal death occurring at >20 weeks' gestation in relation to PCE exposure using town-level exposure data.[56,66] In contrast, a cross-sectional study from Woburn Massachusetts found an increased risk of fetal loss among women with exposure to PCE and TCE contaminated well water; however, its results are difficult to interpret due to deficiencies in the study design and interpretation.[57] Taken together, the current literature indicates that high PCE exposure levels in occupational settings may increase the risk of pregnancy loss but does not provide strong evidence of an overall increased risk of pregnancy loss from exposure to contaminated drinking water.

Results and discussion for ischemic placental disease[17]

Ischemic placental disease is a group of pregnancy disorders thought to have a common etiology through inadequate placental vascular development. The designation includes placental abruption or separation, pre-eclampsia, small for gestational age, and stillbirth. Our study found that PCE exposure was not associated with ischemic placental disease overall (RR: 0.90, 95% CI: 0.65–1.24); however, pregnancies with PCE exposure above the median had 2.38 times the risk of stillbirth at ≥27 weeks' gestation (95% CI: 1.01–5.59) and 1.35 times the risk of placental abruption (95% CI: 0.68–2.67). Because these associations were based a small number of cases, these suggestive findings were re-assessed in the BU Children's Health Study.

Results and discussion for congenital anomalies[20]

Our study found that the risk of certain congenital anomalies was increased among the offspring of women exposed to PCE-contaminated drinking water. Children whose mothers had high exposure levels (>75th percentile) around conception had increased odds of all anomalies combined (OR: 1.5, 95% CI: 0.9–2.5). Increased odds were also observed for neural tube defects (OR: 3.5, 95% CI: 0.8–14.0), oral clefts (OR: 3.2, 95% CI: 0.7–15.0), and genitourinary defects (OR: 1.6, 95% CI: 0.6–3.8) among offspring with any prenatal exposure. Because these results were based on a small number of congenital anomaly cases, we followed up these suggestive findings with a case-control study ("BU Children's Health Study"), better suited for studying rare health outcomes.

BU Children's Health Study methods

The BU Children's Health Study was population-based case-control study was conducted from 2012 through 2017 with funding from the NIEHS Superfund Research Program and the approval of the Institutional Review Boards of Boston University Medical Cancer, the Massachusetts Department of Public Health, and Rhode Island Department of Health.

Identification of subjects

The case-control study extended its catchment area and case ascertainment period to maximize the size of the case groups. Cases were live- and stillborn infants delivered from 1968 through 1995 to mothers who resided in 28 Massachusetts and Rhode Island communities with some VL/AC pipes.[21,22] Infants with (a) central nervous system defects (N = 268), including spina bifida and anencephaly; oral clefts (N = 112); and hypospadias (N = 94); and (b) stillborn infants at ≥20 weeks gestation and/or weighing ≥350 grams whose death was due to placental abruption and/or placental insufficiency (N = 296) comprised the case groups. Controls were randomly selected live-born infants who were delivered during the same time period and geographic area as the cases (target N = 800).

Data collection

Vital records were abstracted to obtain parent's and infant's names; maternal address at delivery; infant's date of birth; parent's age, race and educational level; maternal pregnancy history; date of last menstrual period; prenatal care information, and, if applicable, birth defect diagnoses and cause of death information.[21,22] Mothers were traced using internet

resources and sent a self-administered questionnaire to augment vital records data on confounding variables and obtain information on water source. About 84% of birth defect case mothers, 72% of stillbirth case mothers, and 82% of control mothers were found alive and successfully located. Of these, 39% of birth defects case mothers, 35% of stillbirth case mothers, and 32% of control mothers returned the study questionnaire.

Geocoding and PCE exposure assessment

Nearly 99% of birth addresses were successfully geocoded using ArcGIS 10.0 (ESRI, Redlands, CA).[21,22] PCE exposure assessments followed the methods developed for our cohort study.[18]

Data analysis

The primary analysis of associations between case/control status and prenatal PCE exposure first compared ever exposed *vs.* unexposed mothers.[21,22] Next, PCE exposure quartiles were examined to investigate possible dose-response relationships. Odds ratios estimated the magnitude of these associations and 95% confidence intervals assessed their precision. Potential confounding variables included year and state of delivery, demographic characteristics and known risk factors for stillbirths and birth defects. Multiple imputation was used to obtain values of confounding variables with missing data.

BU Children's Health Study results and discussion

Characteristics of participants

Mothers of cases and controls were predominantly white and 27 years old, on average, when the infant was delivered (Table 3).[21] Similar proportions of case and control mothers were college-educated, drank alcoholic beverages, smoked cigarettes, and initiated prenatal care during the first trimester. There were notable differences in case ascertainment between Massachusetts and Rhode Island and over time (Table 3) and so these variables were controlled in the adjusted analysis. A higher proportion of males among the birth defect cases stemmed from the inclusion of hypospadias, a male genital defect.

Results and discussion for birth defects[21]

Concordant with prior findings from the Cape Cod Health Study,[20] mothers with high exposure levels during the first trimester (>1.136 grams) had increased odds of having a child with spina bifida (OR: 2.0, 95% CI: 0.8–5.4), cleft lip with and without cleft palate (OR: 3.8, 95% CI: 1.2–12.3), and hypospadias (OR: 2.1, 95% CI: 0.5–8.3). No increase in odds of anencephaly was observed in relation to high exposure levels (>1.136 grams).

Our birth defects findings are consistent with animal experiments[25,26] and occupational studies that found positive associations between prenatal exposure to organic solvents and the risk of congenital anomalies, including oral clefts, neural tube defects and cardiac defects.[67–72] The literature examining women exposed *via* contaminated air and drinking water has less consistent results, with five studies reporting increases in the risk of birth defects associated with PCE and/or TCE exposure[56,73–76] while three reported null findings.[57,74,77] For example, a 1995 New Jersey study found that PCE drinking water levels in

excess of 10 ppb were associated with a 3.5-fold increased risk of oral clefts (90% CI: 1.3–8.8), TCE drinking water levels >5 ppb were associated with a 2.2-fold increased risk of oral clefts (90% CI: 1.2–4.2), and TCE levels >10 ppb were associated with a 2.5-fold increased risk of neural tube defects (90% CI: 0.9–6.4).[56] In contrast, a study from Marine Corps Base Camp Lejeune found a 2.4-fold increased odds of neural tube defects in relation to TCE exposure levels >5 ppb (95% CI: 0.6–9.6) but no associations between neural tube defects or oral clefts and any level of PCE exposure.[74]

Taken together, the preponderance of positive associations (including our own) suggests that pregnant women with high levels of exposure to PCE and TCE in occupational and community settings have increased odds of having a child with certain birth defects, including neural tube defects and oral clefts.

Results and discussion for stillbirth[22]

Exposed mothers had a linear dose-dependent increase in the odds of stillbirth due to placental abruption and placental insufficiency. In comparison to unexposed mothers, stillbirth ORs were 1.5 (95% CI: 1.0–2.3) for low exposure (>0-median), 1.7 (95% CI: 1.1–2.5) for moderate exposure (>median-90th percentile), and 1.9 (95% CI: 1.1–3.2) for high exposure (>90th percentile) (p value for trend = 0.02).

These findings are concordant with animal experiments in many species[24,42,60,62,78–81] and occupational studies that found increases in the overall risk of pregnancy loss.[27–29,45,63–65] The only two previous reports that examined late pregnancy loss following exposure to contaminated drinking water have divergent results. In New Jersey, no association was reported in a cross-sectional study of town-level PCE and fetal deaths occurring at ≥20 weeks' gestation where maximum monthly exposure levels were 55 ppb for TCE and 26 ppb for PCE.[56] In contrast, a study in Woburn found a 1.8-fold increased risk of fetal death at ≥20 weeks' gestation among residents with any exposure to solvent contaminated well water during pregnancy (95% CI: 0.4–6.6), and a 2.6-fold increased risk of fetal deaths (95% CI: 0.7–8.9) among women highly exposed during pregnancy (>90th percentile).[57,66] Again, the latter study is difficult to interpret due to deficiencies in the study design. Taken together, the sparse literature suggests that exposure to high PCE levels in occupational settings increases the risk of stillbirth but that drinking water exposures do not increase its overall risk. However, our study results suggest that PCE may increase the risk of stillbirth related to placental dysfunction.

Strengths and limitations of the Cape Cod and BU Children's Health Studies

Like John Snow's cholera investigation in 1854 London,[8] the Cape Cod and BU Children's Studies demonstrate how scientists can take advantage of a "natural experiment" to learn about the reproductive and developmental effects of environmental pollution. The unique circumstances that led to the contamination of the public water supplies in Massachusetts and Rhode Island presented both strengths and hurdles for carrying out this research.[82]

While there is now substantial evidence to support PCE's designation as a probable or likely human carcinogen, its cancer-causing potential was suspected in 1980 when the water contamination came to light.[83–85] Thus, the discovery that PCE was leaching into public water supplies prompted state and local authorities to conduct an investigation of the extent of the contamination and develop a remediation plan. The thorough investigation resulted in a large repository of water system records without which our research would have been impossible. More specifically, the data on pipe locations and installation years enabled the utilization of a sophisticated model to reconstruct historical contaminant levels in drinking water and assign them to individual subjects. These modelling methods have been used in only a few epidemiological studies of historical exposures (*e.g.*, the previously described studies at Marine Corps Base Camp Lejeune) but should be considered in future studies since exposure data gathered from participants are likely to be inaccurate. In fact, we found little agreement between the women's self-assessed exposure status to that derived from the EPANET assessment, given the long length of time between the pollution episode and our data collection efforts.[19]

The widespread nature and irregular pattern of contamination were also fortuitous circumstances for our studies. First, the high exposure prevalence made it feasible to identify sufficient numbers of exposed participants. Second, because VL/AC pipes were installed in response to expansion and replacement needs in a town's water system, adjacent streets and even adjacent houses had different types of pipes and thus different exposure levels (see Fig. 1), resulting in minimal confounding by participant characteristics. This also meant that PCE exposures were not correlated with other environmental contaminants. The diverse settings where VL/AC pipes were installed, for example high water flow locations along main thoroughfares and low water flow areas such as dead-end streets, also led to a wide range of exposure levels, another serendipitous circumstance of our studies. Thus, key strengths were availability of historical data on affected water systems, a relatively high exposure prevalence and wide range of exposure levels, and little opportunity for differential recall bias and confounding.

Nevertheless, conducting these studies also presented considerable challenges that arose from the historical nature of the exposure assessments. These assessments could not account for behavioral characteristics such as water consumption and bathing patterns during pregnancy because they were poorly recalled, and necessitated several assumptions (for example, we assumed that each parcel represented a residence and that all residences had equal water use), both of which likely led to non-differential exposure misclassification and attenuated associations.

We were fortunate to locate a small number of drinking water sample test results from 1980 for comparison with our modeled exposure assessments. While these historical samples were not a "gold standard" because they were used to give a rough indication of where a problem existed and how severe it was, we found good correlation between our modeled estimates and PCE concentrations in the historical water samples,[34] bolstering our confidence in our assessments and suggesting that the extent of exposure misclassification was relatively modest.

Lastly, while several thousand mothers were identified for the cohort study, response rates and resulting frequencies of birth defects and stillbirths were low; thus, a case-control study conducted in a wider geographic area and over a longer time period was necessary to produce more precise findings.

Conclusions

PCE is a widespread environmental and occupational contaminant.[1–3] While animal experiments[23–26] and occupational studies among humans[27–29] suggest adverse impacts on reproduction, few studies have examined reproductive impacts of lower exposure levels observed in community settings. An unusual scenario that resulted in PCE contamination of the drinking water in Massachusetts and Rhode Island afforded a unique opportunity to examine the reproductive effects of environmental PCE exposure. Our studies found that prenatal exposure to PCE-contaminated drinking water is associated with delayed time-to-pregnancy, and increased risks of placental abruption, stillbirths stemming from placental dysfunction, and certain birth defects (Table 4). No associations were observed with pregnancy loss, birth weight, and gestational duration. This research highlights the importance of considering pregnant women and their developing fetuses when monitoring, regulating, and remediating drinking water contaminants thereby ensuring that public drinking water supplies in the U.S. are safe for all to consume.

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Environmental significance

While tetrachloroethylene (PCE) is a common environmental contaminant, there is little information on its reproductive and developmental effects in community settings. Our epidemiological research on the health effects of prenatal exposure to PCE-contaminated drinking water found associations with delayed time-to-pregnancy, and increased risks of placental abruption, stillbirths stemming from placental dysfunction, and certain birth defects. Our research underscores the need for comprehensive environmental regulations to ensure that U.S. drinking water supplies are safe for all to consume.

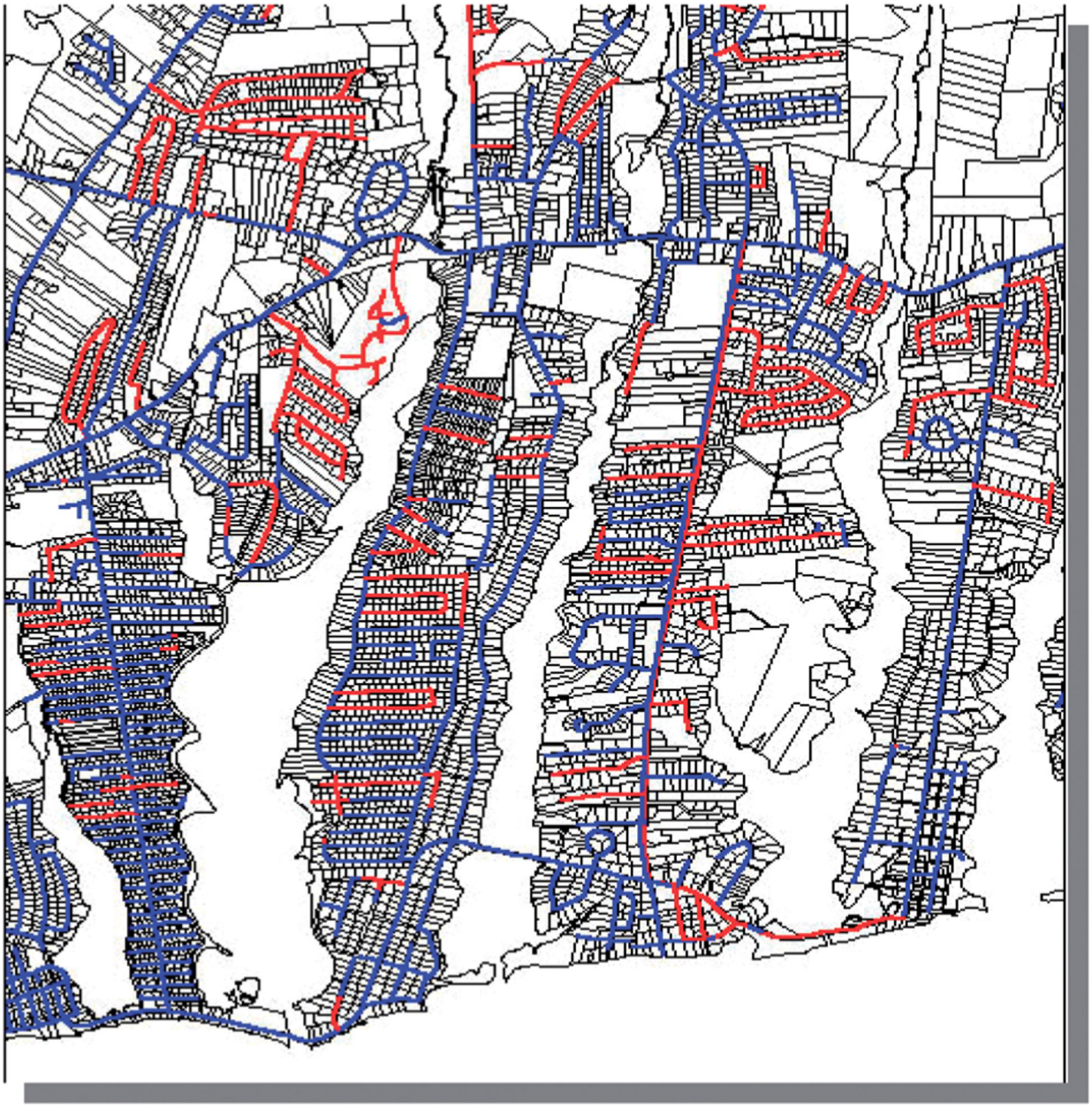

Fig. 1.

Irregular pattern of VL/AC pipes serving parcels in Cape Cod, Massachusetts, USA. Key: vinyl-lined pipe, unlined pipe

Table 1

Distribution of selected characteristics[a] of exposed and unexposed mothers[b] in the Cape Cod Health Study

	Exposed		Unexposed	
	N = 1353		*N* = 772	
Characteristic	***n***	**%**	***n***	**%**
Year of birth				
1969–1973	136	10.1	100	13.0
1974–1978	446	33.0	246	31.9
1979–1983	771	57.0	426	55.2
Age, mean (sd)	27.5 (4.5)		27.6 (4.6)	
White race	1291	95.4	752	97.4
Educational level				
High school graduate or less	536	39.6	294	38.1
Some college	404	29.9	253	32.8
Four year college grad or higher	413	30.5	225	29.1
Prenatal care				
Adequate	989	88.1	555	87.7
Less than adequate	134	11.9	78	12.3
Missing	230		139	
Smoked cigarettes during pregnancy				
Yes	354	26.7	219	28.9
No	973	73.3	539	71.1
Missing	26		14	
Drank alcoholic beverages during pregnancy				
Yes	521	39.5	301	39.6
No	799	60.5	459	60.4
Missing	33		12	
Infant's sex				
Male	693	51.2	378	49.0
Female	660	48.8	394	51.0

[a] Adapted from ref. 18.

[b] Ever exposed or unexposed before birth of index child. Exposure status was based on a leaching and transport model that estimated the annual mass of PCE delivered to each mother's residence.

Table 2

Distribution of cumulative PCE exposure (grams) before pregnancy and average monthly exposure (grams) around time of conception[a]

	Cumulative exposur	Average monthly exposure
Minimum	2.8×10^{-4}	1.2×10^{-4}
10th percentile	1.1	4.0×10^{-2}
25th percentile	5.6	0.2
Median	29.9	0.9
75th percentile	120.0	3.0
90th percentile	334.2	7.9
Maximum	3904.2	147.6

[a]Data come from analyses of birth weight and gestational duration among index births (ref. 18). 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 (whichever came later) through the month and year of the last menstrual period (LMP). Average monthly exposure around the time of conception was estimated by dividing the annual exposure during the LMP year by 12.

Table 3

Distribution of selected characteristics of cases and controls in the BU Children's Health Study[a]

	Birth defect Cases[b] (*N* = 474)		Stillbirth Cases (*N* = 296)		Liveborn Controls (*N* = 771)	
Characteristic	***n***	**%**	***n***	**%**	***n***	**%**
Maternal residence at delivery						
Massachusetts	333	70.3	155	52.4	436	56.5
Rhode Island	141	29.7	141	47.6	335	43.5
Maternal age at delivery (mean, sd)	27.3 (5.7)		27.0 (5.9)		27.0 (5.4)	
Year of delivery						
1969–1978	132	27.8	165	55.7	275	35.7
1979–1988	160	33.8	79	26.7	290	37.6
1989–1995	182	38.4	52	17.6	206	26.7
Missing	3		1		0	
Maternal race						
White	381	92.3	153	91.6	613	90.1
Non-white	32	7.7	14	8.4	67	9.9
Missing	61		129		91	
Maternal educational level						
High school graduate or less	225	55.4	76	51.1	340	50.7
Some college	94	23.2	28	18.8	172	25.7
College graduate	87	21.4	45	30.2	158	23.6
Missing	68		147		101	
Prenatal care began in first trimester						
Yes	336	88.9	94	81.7	473	87.9
No	42	11.1	21	18.3	65	12.1
Missing	96		181		233	
Prenatal cigarette smoking						
Yes	62	22.5	18	31.0	70	24.3
No	214	77.5	40	69.0	218	75.7

Characteristic	Birth defect Cases[b] (*N* = 474) *n*	%	Stillbirth Cases (*N* = 296) *n*	%	Liveborn Controls (*N* = 771) *n*	%
Missing	198		238		483	
Prenatal alcoholic beverage consumption						
Yes	47	31.8	17	29.8	69	35.6
No	101	68.2	40	70.2	125	64.4
Missing	326		239		577	
Infant sex						
Male	290	61.6	—		408	52.9
Female	181	38.4	—		363	47.1
Missing	3		—		0	

[a] Adapted from ref. 21 and 22.

[b] Includes neural tube defects, oral clefts and hypospadias.

Table 4

Summary of reproductive health effects of prenatal exposure to tetrachloroethylene-contaminated drinking water in the Cape Cod and BU Children's Health Studies

Reproductive outcome	Main finding
Time-to-pregnancy	High exposure levels associated with a 1.36-fold increased risk of delayed time-to-pregnancy (95% CI: 1.06–1.76)
Pregnancy loss	Null associations
Birth weight	Null associations
Gestational duration	Null associations
Ischemic placental disease	No overall association with ischemic placental disease. High exposure levels associated with two specific categories of ischemic placental disease: 1.35-fold increased risk of placental abruption (95% CI: 0.68–2.67) and 2.38-fold increased risk of stillbirths (95% CI: 1.01–5.59)
Birth Defects	High exposure levels associated with a 2.0-fold increased odds of spina bifida (95% CI: 0.8–5.4), a 3.8-fold increased odds of oral clefts (95% CI: 1.2–12.3) and a 2.1-fold increased odds of hypospadias (95% CI: 0.5–8.3). Null association for anencephaly
Placenta-related stillbirths	Dose-dependent increases in odds of stillbirth due to placental abruption and placental insufficiency. Odds increased from 1.5 (95% CI: 1.0–2.3) for low exposure, 1.7 (95% CI: 1.1–2.5) for moderate exposure, and 1.9 (95% CI: 1.1–3.2) for high exposure