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Risk of Learning and Behavioral Disorders Following Prenatal and Early Postnatal Exposure to Tetrachloroethylene (PCE)-contaminated Drinking Water

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Abstract

This population-based retrospective cohort study examined the association between developmental disorders of learning, attention and behavior and prenatal and early postnatal drinking water exposure to tetrachloroethylene (PCE) on Cape Cod, Massachusetts. Subjects were identified through birth records from 1969 through 1983. Exposure was modeled using information from town water departments, a PCE leaching and transport algorithm, EPANet water flow modeling software, and a Geographic Information System (GIS). Mothers completed a questionnaire on disorders of attention, learning and behavior in their children and on potential confounding variables. The final cohort consisted of 2,086 children. Results of crude and multivariate analyses showed no association between prenatal exposure and receiving tutoring for reading or math, being placed on an Individual Education Plan, or repeating a school grade (adjusted Odds Ratios (OR)=1.0–1.2). There was also no consistent pattern of increased risk for receiving a diagnosis of Attention Deficit Disorder (ADD) or Hyperactive Disorder (HD), special class placement for academic or behavioral problems, or lower educational attainment. Modest associations were observed for the latter outcomes only in the low exposure group (e.g., adjusted ORs for ADD were 1.4 and 1.0 for low and high exposure, respectively). (All ORs are based on an unexposed referent group.) Results for postnatal exposure through age five years were similar to those for prenatal exposure. We conclude that prenatal and early postnatal PCE exposure is not associated with disorders of attention, learning and behavior identified on the basis of questionnaire responses and at the exposure levels experienced by this population.

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Conflict of Interest

All authors (Patricia Janulewicz, Roberta White, Michael Winter, Janice Weinberg, Lisa Gallagher, Veronica Vieira, Thomas Webster, and Ann Aschengrau) attest to having no conflict of interest.

Keywords

Tetrachloroethylene; PCE; development; contaminated water; learning disabilities

1. Introduction

Tetrachloroethylene (PCE, Perc or perchloroethylene) is a manufactured chemical used mainly for fabric dry cleaning and metal degreasing. PCE is one of the most commonly detected solvents in groundwater¹ and at United States Environmental Protection Agency (USEPA) Superfund sites². As of 1997, 771 National Priority List (NPL) sites around the United States had evidence of PCE contamination². In addition, PCE had been found in 38% of the 9,232 surface water sampling sites in the United States².

PCE and its main metabolite dichloroacetylene (DCA) are recognized human and animal neurotoxins^{3–7}. These fat soluble substances have a high affinity for the lipophilic tissues of the central nervous system⁸. PCE also readily crosses both the placental and blood brain barriers⁵.

Most of the relevant epidemiological literature has examined neurological sequelae among adults with occupational exposures to mixtures of organic solvents. Impairments in cognition and vision have been observed, as have mood changes^{9–25}. The cognitive sequelae observed following mixed organic solvent exposures included diminished performance on measures of memory, attention/executive function, and motor skills. The results from the few studies examining adult occupational exposures to only PCE are mixed. Some studies found diminished performance on measures of attention/executive function among the PCE exposed subjects compared to unexposed controls [3,24,55,56], while other studies did not find adverse effects [21,24]. All studies that examined visuospatial abilities found a diminished performance in the PCE exposed group compared to unexposed controls [3,21,55].

The maturation of the nervous system is more complex than any other organ, thus making it exquisitely vulnerable to chemical insults. Depending on timing, type, and dose, an exposure occurring during the developmental period can result in long-term alterations in brain structure and function. The vulnerable window for neurotoxic agents is long, extending from the prenatal period through adolescence and early adulthood. The functional domains of the nervous system (language, visuospatial, learning and memory and motor abilities) develop at different times with different windows of vulnerability and different sensitivities to environmental agents^{26–35}.

To date, three studies have examined effects of maternal occupational mixed solvent exposure during the prenatal period on neurodevelopment. The study by Eskanazi et al.³⁶ showed no significant difference in general mental abilities, using the McCarthy Scales of Children's Abilities, between exposed and unexposed children at ages 3–4 years. Domain specific functions (i.e. memory or language specific tests) were not examined.

In contrast, Till et al.³⁷ found that prenatal maternal exposure to organic solvent mixtures was associated with worse performance on measures of expressive and receptive language, and reduced graphomotor skills (using NEPSY tests) among children at ages 3–7 years. Study parents also rated exposed children as having more behavioral problems on the child behavior checklist than unexposed children.

Laslo-Baker et al.³⁸ examined children exposed to organic solvent mixtures during the prenatal period and neurobehavioral performance at ages 3–7 years. Exposed children scored lower on neurobehavioral tests of general intelligence, language and motor abilities. General intelligence

was assessed with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and Wechsler Intelligence Scale for Children III (WISC III). Language was assessed using the Preschool Language Scale 3 (PSL 3) and Clinical Evaluation of Language Fundamentals 3 (CELF 3). Motor abilities were assessed with the grooved pegboard test.

Unlike the occupational studies described above, the present study examined PCE exposure from an unusual environmental scenario. In early 1980 it was discovered that PCE had been leaching into the drinking water supplies of many New England towns during the previous 15 years. Investigations revealed that the public water distribution systems in many of these towns had installed vinyl-lined asbestos-cement (VL/AC) pipes and that PCE had leached into the water from the liner. Approximately 660 miles of these pipes were installed in Massachusetts from 1968 through early 1980; a large proportion was installed in eight Cape Cod towns³⁹ (Figure 1). The pipe manufacturing practice involved spraying a mixture of vinyl toluene resin and PCE onto the interior of the pipe. It was believed that the PCE would volatilize and disappear before the pipes were installed. However, PCE measurements taken in 1980 from Cape Cod public drinking water supplies ranged from 1.5 µg/L to 7,750 µg/L⁴⁰. State officials decided that the most appropriate remedy was to flush and bleed the VL/AC pipes in order to reduce the PCE concentrations to levels determined to be safe at the time. The 1980 action level was set to 40 µg/L to address this problem; the current United States Environmental Protection Agency (USEPA) maximum contaminant level (MCL) is 5 µg/L⁴.

This scenario presented a unique and valuable setting for examining the health effects of PCE exposure because many people were exposed to a large range of levels, and other water contaminants were rare. Furthermore, the VL/AC pipes were irregularly distributed according to the replacement and expansion needs of the towns. As part of a population-based study that examined the connection between exposure to PCE-contaminated drinking water and adverse reproductive and developmental outcomes, the current study investigated the impact of prenatal and early postnatal PCE exposure on learning, attention and behavior.

2. Material and Methods

2.1. Study Population Selection

All children born between 1969 and 1983 whose mothers lived in one of eight Cape Cod towns with VL/AC water distribution pipes at the time of birth were eligible for the study. These towns were Barnstable, Brewster, Bourne, Chatham, Falmouth, Mashpee, Provincetown, and Sandwich (Figure 1). Eligible children were identified by reviewing Massachusetts birth certificates. The residence listed on the birth certificate was crossmatched with a database of all street locations with VL/AC pipes to tentatively designate a subject as “exposed” or “unexposed.” This tentative designation was based on visual inspection of the maps of water pipe distribution in the immediate vicinity of the birth residence. The database contained information on the location, installation year, and diameter of the pipes.

Two groups of children were selected: 1) children who were tentatively designated as “exposed” to PCE prenatally 2) children who were tentatively designated as “unexposed” to PCE prenatally. Based on the initial exposure designation, 1,910 “exposed” children and 1,928 “unexposed” children were selected for enrollment. The “unexposed” children were randomly selected and were frequency matched to exposed children on the month and year of birth. The “exposed” group comprised 1,862 singleton births and 24 sets of twins. The “unexposed” group consisted of 1,853 singleton births and 37 sets of twins or triplets. More extensive exposure assessments were conducted following the return of self-administered questionnaires which included detailed residential histories as well as information on the drinking water source.

2.2. Follow up and Enrollment

Mothers (or fathers, if the mother was deceased) were traced to find current addresses and phone numbers using Massachusetts residence lists; death, marriage, divorce, credit bureau and alumni records; telephone books, directory assistance, and the Internet White Pages. Recruitment letters explaining the purpose of the study and accompanying self-administered questionnaires were sent to all traced parents. Eight percent of the selected population was not located, 17.1% were located but never responded to any contact attempts (4 attempts were made by mail and telephone) and 9.1% refused to participate (Table 1). Another 0.2% of the subjects were deemed ineligible, primarily because the birth certificate address was later found to be a temporary residence. These percentages were similar for both the exposed and unexposed groups. In all, 1,240 exposed and 1,250 unexposed subjects were enrolled and returned the study questionnaires.

The non-participants were similar to participants with regard to the distribution of births, the child's sex, race, and prevalence of children who were born with low birth weight or prematurely. Non-participating mothers were younger (mean age 26.0 years), less educated (11.3% did not graduate from high school) and had more prior births (51.1% had three or more prior births) than participating mothers (mean age 27.5 years, 3.6% did not graduate from high school, and 24.3% had three or more prior births). These differences held true for both exposed and unexposed non-participants. For example, 11.2% vs. 11.4% of exposed and unexposed non-participants did not graduate high school, and 52.9% and 49.3% of exposed and unexposed non-participants had three or more prior births.

2.3. Data Collection

Review of birth certificates provided information on child's date of birth, gestational duration and birth weight and parents' ages, occupations and educational level. Self-administered questionnaires, filled out by the mother in 2002–2003 (or father, if the mother was deceased) were used to gather information on developmental and educational histories and learning and behavioral disorders in the child, as well as possible confounders and residential history. Questions determined if the child ever received a diagnosis of Attention Deficit Disorder (ADD) or Hyperactive Disorder (HD), tutoring for math or reading, a special class placement for academic or behavioral problems, an Individual Education Plan (IEP) from the school system; and if the child ever repeated a school grade. Highest level of educational attainment of the child was also obtained; all children were old enough to have completed high school by the time the questionnaire was administered.

Demographic information collected about the parents included race, marital status, age at time of the child's birth, educational and occupational histories including current occupation and highest level of education achieved, as well as history of learning difficulties. Information on parental age, education and occupation was also collected from the birth certificate. The primary source of information on these three variables was the birth certificate; missing birth certificate information was filled in with the questionnaire data. Maternal medical history information was collected from the questionnaire on diseases before and during pregnancy, including diabetes and high blood pressure; pregnancy complications including gestational diabetes and preeclampsia; use of legal and illicit drugs, and vitamins and iron supplements during pregnancy. Birth weight and gestational age were obtained from the birth certificate. Other information on child's medical history was collected from the self-administered questionnaire, including a breast feeding history, and the presence of birth defects, severe mental retardation, cerebral palsy, fetal alcohol syndrome and lead poisoning. Questions about the use of professional dry cleaners, spot removers, and occupations provided information on other potential sources of solvent exposure. Information on water sources, uses of water treatment devices, and tap and bottle water; and bathing habits were also collected.

2.4. PCE Exposure Assessment

As described previously, children received tentative exposure designations using a visual inspection of maps of the pipe distribution network in the immediate vicinity of the birth address. To determine a child's final exposure designation, information was integrated from several additional sources. Along with information from town water departments on the location of vinyl-lined pipes, other sources incorporated into the exposure assessment included: 1) a Geographic Information System (GIS, ArcGIS 8.1) to spatially locate the vinyl-lined pipes and the residences; 2) EPANET water distribution system modeling software to model water flow and direction; and 3) a leaching and transport model to estimate the amount (grams) of PCE that was delivered to each reported residence during the prenatal and postnatal periods. The leaching and transport model was developed by Webler and Brown^{41,42} and the leaching rate was estimated from experiments by Demond⁴⁰. The Webler and Brown model estimates the amount of PCE entering the drinking water using information on the initial PCE stock in the pipe liner, the pipe's age, and the leaching rate of PCE from Demond's experiments. The pipe's initial stock of PCE was based on the size of the pipe (e.g., diameter, length) and information from the pipe manufacturer on the application of the liner. The EPANET software was developed by the U.S. Environmental Protection Agency and has been used in multiple epidemiologic studies^{43–47}. Study subjects may be exposed to PCE in drinking water either through ingestion, dermal absorption and inhalation, particularly during bathing⁴⁸. However, we did not consider questionnaire data on water consumption and bathing habits decades before to be reliable enough to further refine the exposure measure. Instead, exposures values represent the modeled cumulative mass of PCE entering the homes of study participants and are not a direct measure of PCE intake by the subjects. For example, the modeled cumulative mass of PCE was diluted before entering the home in an estimated 90,000 gallons of water used by an average household in a year. We assumed that all users on the water distribution network drew the same amount of water because the study area consisted mostly of residences. We also assumed that water sources did not change over the study period. The distribution systems that were in place by the 1960s and early 1970s remained generally unchanged until population growth during the 1980s required some systems to expand and add water sources. Our model was applied to the water distribution system conditions in 1980, near the end of the study period.

PCE exposure levels were calculated for 94.8% of the study children who had completely geocoded residential histories and information on their mother's last menstrual period (LMP). The LMP was based on birth certificate information on date of birth and gestational duration. There were inadequate residential histories for 182 children and missing information on LMP for 19 children (Table 1). Cumulative exposure to PCE in grams was calculated by summing the amount of PCE delivered to each subject's residence during two periods of interest. Cumulative exposure for the prenatal period was measured from the month and year of the LMP through the month and year of birth. Cumulative exposure for the early postnatal period was measured from the month and year of the child's birth through the month and year of his/her fifth birthday.

2.5. Statistical Analysis

Separate analyses were conducted evaluating the effects of PCE exposure during the prenatal period and early postnatal period. The prenatal period analysis compared subjects whose residential drinking water was contaminated with PCE during the prenatal period to those whose drinking water was, according to the exposure assessment, free of PCE contamination during the prenatal period. The postnatal period analysis compared subjects whose residential drinking water was contaminated with PCE during the five-year postnatal period to those whose water was uncontaminated during this period. Prenatal and postnatal PCE exposures were

highly correlated (Spearman correlation coefficient 0.87, p-value <.0001). Therefore, we could not examine prenatal exposure while taking into account postnatal exposure and vice versa.

A locally weighted regression smoother (LOESS) was used to determine the shape of the relationship between the exposures and outcomes⁴⁹. The results suggested no natural cut points for the exposure. Therefore, other logical cut points were derived to designate “low” and “high” exposure (in addition to no exposure). For the prenatal period analysis, a cut point of 10 g for the nine month exposure period was used. For the postnatal period, a cut point of 66.7 g for the five year exposure period was used. Given the duration of exposure and using a typical household water use over a year (90,000 gallons/year), these cut points correspond to being exposed to an average drinking water concentration of 40 ug/L, the suggested action level when the contamination was discovered in 1980, for nine months and five years respectively.

A total of 404 subjects were excluded from the analyses because they fell into one or more of the following categories (Table 1): multiple birth; died before age 21 years; diagnosed with lead poisoning, fetal alcohol syndrome, mental retardation, or cerebral palsy; prenatal exposure to a known teratogen; daily or weekly marijuana use; 7+ drinks of alcoholic beverages per week during the prenatal period; or non-calculable exposure. These exclusions were made because of the known associations between these variables and the outcomes under investigation. Children who died before the age of 21 were excluded because they were unlikely to have attained their highest level of education.

The following eight measures of learning, attention and behavior were examined: whether the child ever had a diagnosis of Attention Deficit Disorder (ADD) or Hyperactive Disorder (HD), received tutoring for reading or math, had special class placement for academic or behavioral problems, had an Individual Education Plan, repeated a school grade, and the highest level of education achieved. Each outcome was defined as a dichotomous variable (yes or no, for most variables). Highest level of education was divided into high school degree or less and more than a high school degree. There was minimal loss of information due to missing outcome data for either the prenatal (2.3%–5.9%) or postnatal (2.1% – 5.6%) analyses.

Because many mothers had more than one child in the study (16% had two or more births), generalized estimating equation (GEE) analyses with a logit link function were used to account for potential correlation between sibling outcomes. For all analyses, odds ratios (ORs) were used to measure the strength of the associations and 95% confidence intervals were used to assess their statistical stability. An unexposed group was used as the reference category in all analyses.

First, a crude OR was calculated without adjusting for potential confounders or accounting for the correlation between children. Next, a simple GEE analysis was conducted to account for the non-independent outcomes arising from multiple siblings. Lastly, a multivariate GEE analysis was conducted to control for confounding variables. Six core variables were included in all multivariate models --maternal age, education and race, and child's sex, and a combined variable based on birth weight and gestational duration-- because of their known association with the outcomes. Birth weight and gestational duration were highly correlated, so a combined variable was created designating low birth weight and/or premature birth. The remaining possible confounders (maternal learning history; paternal education and occupation; maternal smoking, alcohol, and marijuana use during pregnancy, pregnancy complications, pregnancy induced high blood pressure and pre-eclampsia, gestational and non gestational diabetes, viral infection during pregnancy) were entered into the model one at a time so that we could compare the two sets of multivariate GEE odds ratios⁵⁰. This procedure revealed that no additional variables changed the core-adjusted odds ratios by more than 10%, and so no additional variables were included in the final multivariate models.

Criteria related to model fit were not applied for two reasons: First, our goal was to examine the relationship between PCE exposure and disorders of learning and attention while controlling for confounding and not to find the best fitting model. Secondly, our dichotomous outcomes limited the number of confounders we could practically include in our model.

Stratified analyses were also conducted to determine if there was effect measure modification by the following characteristics: child's sex (male/female), occupational solvent exposure during pregnancy (yes/no), alcohol use during pregnancy (1–3 drinks per month or less/ 1–2 drinks per week or more), smoking during pregnancy (none/ 10 cigarettes a day or less/ 10+ cigarettes a day), caffeine intake during pregnancy (less than 3 cups per day/ 3+ cups per day), breast feeding (yes/no), tap water use during pregnancy (less than 4 glasses per day/ 4+ glasses per day), bottled water use during pregnancy (ever/never), and showering habits during pregnancy (ever/never took hot or very hot showers; ever/never showered greater than 70 minutes per week). Past water use such as water consumption and bathing habits may be difficult to recall accurately because these events occurred long ago. Patterns of water use do not also appear to significantly alter an individual's exposure rank because there is insufficient variability in consumption and bathing patterns⁴⁸. Thus, we did not incorporate these factors into our exposure assessment but rather examined them as possible effect modifiers.

3. Results

A total of 2,086 subjects were available for the final analysis. According to the initial exposure designation, there were 1,063 exposed and 1,023 unexposed children. Following the in-depth exposure assessment, there were 1,349 exposed and 737 unexposed children (Table 1). A total of 444 subjects switched exposure groups: 365 unexposed children switched to the exposed group and 79 exposed children switched to unexposed group. The primary reason for switching from the unexposed to exposed group was having a residence down gradient from a VL/AC pipe that was originally considered unexposed by visual inspection. The primary reason for switching from the exposed to unexposed group was questionnaire data indicating that the source of the subject's drinking water was a private well. This information was not available when the original exposure designations were made.

Of the 2,086 subjects available for analysis, 1,349 children had either prenatal or postnatal exposure and 737 children had neither prenatal nor postnatal exposure (Table 1). Subjects in the prenatal analyses included 1,244 subjects with any prenatal exposure and 842 subjects with no prenatal exposure. Subjects in the postnatal analyses included 1,326 subjects with any postnatal exposure and 760 subjects with no postnatal exposure.

There was a wide distribution of estimated exposures during the prenatal and postnatal periods (Table 2). Among exposed individuals, levels ranged from 4×10^{-5} g to 1328g during the prenatal exposure period and from 2.9×10^{-4} g to 3310g during the postnatal exposure period. These values represent the modeled cumulative mass of PCE entering the homes of study participants and are not a direct measure of PCE intake by the subjects. For example, the modeled cumulative mass of PCE was diluted before entering the home in an estimated 90,000 gallons of water used by an average household each year.

The characteristics of the exposed and unexposed groups were, for the most part, very similar (Table 3). The births were equally distributed over the study years because of matching. There was an equal distribution of males and females, low birth weight, preterm and breastfed infants. Mothers in both groups were, on average, 27 years old at the birth, predominately white, and educated beyond high school. There were some differences in paternal occupations. The percent of white collar jobs was higher in the exposed group while the percent of 'other' jobs (which included military jobs) was higher in the unexposed group. The association between

exposure status and 'other' occupations likely arose because a military base located in the study region had an independent water distribution system with no VL/AC pipes. The use of caffeine, alcohol, cigarettes or marijuana during pregnancy was also comparable between the groups. High and similar percentages of women took multivitamins and iron supplements. Because PCE can be smelled in water when levels reach 0.33 mg/L, it is noteworthy that a slightly higher percent of unexposed women reported drinking tap water and a slightly higher percent of exposed women reported drinking bottled water. In addition, a slightly higher percentage of women in the unexposed group took long and hot showers.

There was a wide range of ages at which the study diagnoses and other outcomes occurred. However, the mean age at diagnosis or first occurrence of all assessed outcomes was comparable between the exposed and unexposed groups: diagnosis of ADD (unexposed = 12.5 years, exposed = 11.8 years), diagnosis of HD (unexposed = 10.5 years, exposed = 10 years), tutoring for reading (unexposed = 7.7 years, exposed = 7.6 years), tutoring for math (unexposed = 10.8 years, exposed = 10.7 years), special class placement (unexposed = 8.1 years, exposed = 8.6 years), Individual Education Plan (unexposed = 8.1 years, exposed = 8.6 years), repeated a grade (unexposed = grade 2.2, exposed = grade 2.4).

3.1. Prenatal Analysis Results

The crude, simple and multivariate prenatal analysis results are presented in Table 4. There were no meaningful associations between prenatal PCE exposure and receiving tutoring for reading or math, being placed on an IEP, or repeating a school grade. The pattern of increased risk was inconsistent (e.g., lacked dose response) for receiving a diagnosis of ADD (low exposure multivariate OR 1.4, 95% CI 0.9–2.0; high exposure multivariate OR 1.0, 95% CI 0.7–1.6), or HD (low exposure OR 1.5, 95% CI 0.9–2.7; high exposure OR 0.8, 95% CI 0.4–1.6), special class placement for academic or behavioral problems (low exposure OR 1.3, 95% CI 0.9–1.7; high exposure OR 0.8, 95% CI 0.6–1.2), or lower educational attainment (low exposure OR for high school education less 1.3, 95% CI 1.0–1.7; high exposure OR 1.0, 95% CI 0.8–1.4). The positive associations were modest, statistically unstable, and seen only in the low exposure group.

3.2. Postnatal Analysis Results

The simple, crude and multivariate postnatal analysis results are presented in Table 5. Again, there were no meaningful associations between postnatal PCE exposure and receiving tutoring for reading or math, special class placement for academic or behavioral problems, repeating a grade in school or lower education attainment. As in the prenatal exposure analyses, the pattern of increased risk was inconsistent according to exposure level for several outcomes, including receiving a diagnosis of ADD (low exposure multivariate OR 1.3, 95% CI 0.9–1.9; high exposure multivariate OR 1.0, 95% CI 0.6–1.7), or HD (low exposure OR 1.4, 95% CI 0.8–2.5; high exposure OR 0.7, 95% CI 0.3–1.6), and being placed on an Individual Education Plan (low exposure OR 1.3, 95% CI 1.0–1.8; high exposure OR 0.8, 95% CI 0.6–1.2). Again, the positive associations were modest, statistically unstable, and seen only in the low exposure group.

3.3. Stratified Analysis Results

There was no evidence of effect measure modification by alcoholic beverage consumption during pregnancy or breast feeding. Furthermore, the evidence for effect modification according to the following variables was contrary to our dose-response hypotheses: smoking during pregnancy, caffeine intake during pregnancy, maternal occupational solvent exposure, taking hot or very hot showers, and showering for greater than 70 minutes per week. For example, for the highest level of education achieved, the OR for smoking 10+ cigarettes/day during pregnancy was lower than the ORs for smoking 10 or less cigarettes/day during

pregnancy and not smoking at all during pregnancy (smoking 10+ cigarettes/day during pregnancy OR 0.8; smoking 10 or less cigarettes/day during pregnancy OR 1.9; not smoking during pregnancy OR 1.0). (These results were not presented in a table.)

3.4 Additional Analysis

Since there was a relatively higher prevalence of military personnel among the unexposed group a sensitivity analysis excluding military families was conducted. The ORs did not change for any of the outcomes examined.

4. Discussion

The results of this study suggest that prenatal and early postnatal exposure to PCE are not associated with later disorders of attention, learning and behavior using questionnaire-based outcome measures and at the exposure levels experienced by this study population. While modest associations were seen for some outcomes (i.e., received a diagnosis of ADD or HD, special class placement for academic or behavioral problems, and lower educational attainment, being placed on an IEP), the dose-response pattern was inconsistent because modest associations were seen with the low but not the high exposure group.

Two of the outcomes examined in this study were diagnoses (ADD, HD) while the other outcomes were indicators of learning disabilities. The prevalences of ADD and HD in our population were 8.5% and 3.5%, respectively. Published prevalence rates for ADHD range from 3–12% (with the majority in the 3–5% range) in the U.S. population. The other study outcomes are indicators of learning disabilities with few available statistics and so it is difficult to make comparisons with published norms.

This study was likely affected by both exposure and outcome misclassification. Historical exposures were calculated using a leaching and transport model and a computer simulation program that estimated the mass of PCE delivered to each residence. While preliminary results from a validation study suggest reasonable agreement between the modeled exposure estimates and historical PCE water samples (Spearman correlation coefficient = 0.48, $p < 0.0001$), some non-differential misclassification was likely due to errors in estimating the magnitude and direction of the water flow. While individual exposure may differ due to differences in water ingestion and bathing habits, previous work suggests that taking these factors into account does not change the exposure ranking in a meaningful way⁴⁸. Outcome misclassification also likely occurred because these data were collected through maternal reports on self-administered questionnaires. All sources of misclassification were likely non-differential, that is, misclassification of an outcome variable was unrelated to the exposure, and vice versa. When the exposure classification is dichotomous, non-differential misclassification tends to bias results towards the null. However, when there are three exposure groups as we had (none, low and high), results for the low exposure group may be biased either towards or away from the null, while results for the high exposure group are likely biased toward the null⁵¹. This phenomenon may likely explain why slightly elevated odds ratios were observed only in the low exposure group. While it is likely that there may have been more misclassification in the highly exposed group there would have to be a very large amount of misclassification to produce null results.

Despite these limitations, this study has many strengths. The study population was large, and was exposed to a wide range of PCE levels from an environmental source. In addition, there was little confounding by other water contaminants. Information was available for a large number of important confounding variables from birth certificates and questionnaires. Little difference between the crude and multivariate adjusted results indicates that there was little confounding by the measured covariates and suggests that there is minimal residual

confounding from unmeasured covariates. There was also a minimal loss of subjects from unsuccessful tracing, a high participation rate (73.8%), and little missing data. While non-participants tended to be younger, less educated and have more children than participants, this was true for both exposed and unexposed non-participants and so selection bias was unlikely. Recall bias was also unlikely. While there were news reports in the 1980s reporting the streets where the VL/AC pipes were located, most participants did not accurately report their exposure status on the questionnaire. When asked whether they believed their water was contaminated, 67.7% of the exposed subjects believed their water was contaminated while 32.3% did not believe it was contaminated. Furthermore, 49.4% of the unexposed group believed their water was not contaminated while 50.6% believed it was contaminated.

Two prior epidemiologic studies of pregnant women occupationally exposed to solvents found that the offspring had neuropsychological impairments when tested at ages 3–9 years^{37,38}. These studies by Till et al.³⁷ and Laslo-Baker et al.³⁸ used sensitive measures to assess deficits in brain function and found that exposed children performed worse on measures of general intelligence, expressive and receptive language abilities as well as motor performance as compared to unexposed children. In contrast, one previous epidemiologic study of pregnant women occupationally exposed to solvents found no association with general intelligence among children at ages 3–4 years³⁶. The latter measure used by Eskenazi et al.³⁶ is less sensitive than those used by Till et al.³⁷ and Laslo-Baker et al.³⁸. The present study also investigated only major outcomes of learning, attention and behavior and so we cannot rule out an effect of prenatal and postnatal PCE exposure on more subtle cognitive outcomes.

Our study also differs from the three prior occupational studies in the type and intensity of the exposure. Mixed solvents were examined in the prior studies while a single solvent was examined in the current one. Also, occupational exposures tend to be more intense than environmental ones. Because our population was highly educated, predominately white, and had good access to prenatal care, the present results may not be generalizable to more ethnically diverse and disadvantaged populations.

In summary, there was no consistent relationship between prenatal or early postnatal exposure to PCE and later disorders of learning, attention or behavior as measured by self-administered maternal reports. Results suggest that PCE exposure during these critical periods of brain development does not have an adverse impact on these measures of learning, attention and behavior at the exposure levels experienced in this population. Because PCE remains a commonly used commercial solvent and common ground and surface water contaminant and our study did not employ the most sensitive measures of brain function, it is important to continue to study the impact of prenatal and postnatal exposure. Further studies exploring the adverse impacts of PCE exposure using more sensitive outcome instruments, including neuropsychological testing and brain imaging, are currently underway among this study population.

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Figure 1.
Cape Cod region of Massachusetts with Study Towns Highlighted

Table 1

Selection, Enrollment, Exposure Status and Exclusions of Study Population

	Exposed	Unexposed	Total
Selected	1,910^a	1,928^a	3,838^a
<u>Excluded During Enrollment^a</u>			
Never located or contacted	161	147	308
Located but No response	306	375	681
Ineligible	3	5	8
Refusal	200	151	351
Returned Questionnaire	1,240^a	1,250^a	2,490^a
<u>Excluded During Exposure Assessment^a</u>			
Non calculable residential exposure	76	106	182
Non calculable during pregnancy exposure (unknown LMP) ^d	10	9	19
<u>Excluded During Analysis^a</u>			
Multiple birth	38	55	93
Died before age 21 years	15	18	33
Diagnosed with lead poisoning, mental retardation, cerebral palsy or CNS related malformations	21	16	37
Used known teratogen(s) during pregnancy	11	4	15
Daily or weekly marijuana use during pregnancy and/or 7+ drinks per week during pregnancy	20	34	54
Missing information on any one core confounder	13	11	24
Available for Analysis^{a, c}	1,063^c	1,023^c	2,086^c
<u>Final Exposure Status of subjects available for analysis^b</u>			
Exposed (prenatal and/or postnatal exposure)	984	365	1,349 ^b
Unexposed (neither prenatal nor postnatal exposure)	79	658	737 ^b
	1,063	1,023	2,086^b
Prenatal Exposure Analysis	1,244	842	2,086 ^b
Postnatal Exposure Analysis	1,326	760	2,086 ^b

^a based on initial exposure assessment.^b based on questionnaire data and in depth exposure assessment.^c exclusions² exclusions do not add up to the number available for analysis because some subjects are counted in multiple categories of exclusion.^d unknown LMP or location of residence.

Table 2

Distribution of PCE exposure (grams) for subjects with Prenatal Exposure and Postnatal Exposure

	Prenatal Exposure^a	Postnatal Exposure (birth to age 5)^b
Sample size ^c	1,244	1,326
Minimum	4×10^{-5}	3×10^{-4}
10 th Percentile	0.37	1.00
25 th Percentile	1.82	4.16
Median	7.34	20.34
75 th Percentile	26.62	87.00
90 th Percentile	71.13	232.32
Maximum	1328.00	3309.85

^a 59% of the population was exposed to some amount of PCE during the prenatal period, while 41% were unexposed during the prenatal period.

^b 64% of the population was exposed to some amount of PCE during the postnatal period, while 36% were unexposed during the postnatal period.

^c Unexposed not included in this table.

Table 3**Population Characteristics by Exposure Group**

Characteristic	Exposed (prenatal) n=1,244	Unexposed (prenatal) n=842	Exposed (postnatal) n=1,326	Unexposed (postnatal) n=760
	%	%	%	%
Year of birth				
1969–1973	10.6	11.9	11.1	11.2
1974–1978	33.4	30.8	33.3	30.5
1979–1983	56.0	57.4	55.6	58.3
Sex				
Male	50.6	49.3	50.7	48.9
Female	49.4	50.7	49.3	51.1
Maternal race				
White	95.1	97.9	95.3	97.8
Non-White	4.9	2.1	4.7	2.2
Birth weight				
Low birth weight (<2500 g)	2.3	2.6	2.2	2.8
Normal birth weight (2500+ g)	97.7	97.4	97.8	97.2
Gestation				
Preterm (<37weeks)	4.6	3.7	4.4	3.8
Full term (37+ weeks)	95.4	96.3	95.6	96.2
Breastfed				
Yes	62.1	62.4	61.1	64.1
No	35.0	34.9	36.0	33.3
Unknown	2.9	2.7	2.9	2.6
Maternal age (mean (sd))	27.4 (4.6)	27.6 (4.5)	27.2 (4.6)	27.8 (4.5)
Maternal education				
< High school	4.3	2.7	4.3	2.5
High school grad	35.3	34.9	36.3	33.2
Some college	29.9	32.5	29.3	33.9
4 year college grad or higher	30.5	29.8	30.2	30.4
Paternal occupation				
White collar	51.0	46.3	50.2	47.2
Blue collar	32.8	31.0	33.8	29.1
Other	14.5	21.0	14.5	21.8
Unknown	1.7	1.7	1.6	1.8
Cigarette smoking during pregnancy				
Never smoked during pregnancy	72.0	71.6	71.6	72.4
10 cigarettes or fewer/day	11.7	12.1	11.5	12.4
11–20 cigarettes/day	9.8	10.6	10.1	10.1
21+ cigarettes/day	4.4	4.0	4.8	3.4
Unknown	2.1	1.7	2.0	1.7
Alcohol consumption during pregnancy				
Never drank during pregnancy	59.6	60.7	59.9	60.3
1–3 drinks/month	25.7	24.9	25.7	24.9
1–6 drinks/week	12.1	12.7	11.9	13.2
Unknown	2.6	1.7	2.5	1.7
Occasional marijuana use during pregnancy				
Yes	2.9	2.9	2.9	2.8
No	94.7	95.0	94.6	95.1
Unknown	2.4	2.1	2.4	2.1
Consumption of caffeinated beverages during pregnancy				
3+ cups/day	21.1	19.7	21.3	19.2
<3 cups/day	77.0	78.3	76.8	78.8
Unknown	1.9	2.0	2.0	2.0
Pregnancy complications				
Yes	26.0	24.8	25.7	25.1
No	72.8	74.3	73.1	74.1
Unknown	1.2	0.8	1.2	0.8

Characteristic	Exposed (prenatal) n=1,244 %	Unexposed (prenatal) n=842 %	Exposed (postnatal) n=1,326 %	Unexposed (postnatal) n=760 %
Maternal history of occupational solvent exposure				
Yes	11.7	9.5	11.5	9.6
No	84.2	86.9	84.6	86.6
Unknown	4.0	3.6	3.8	3.8
Maternal multivitamin use during pregnancy				
Yes	92.3	91.3	92.2	91.3
No	5.5	6.3	5.6	6.2
Unknown	2.3	2.4	2.2	2.5
Maternal iron supplementation during pregnancy				
Yes	67.2	64.5	66.7	65.0
No	26.0	29.0	26.4	28.6
Unknown	6.8	6.5	6.9	6.4
Average number glasses of tap water consumed during pregnancy				
>4 glasses/day	40.4	46.3	38.9	49.6
4 or fewer glasses/day	41.4	39.8	42.5	37.6
Unknown	18.2	13.9	18.6	12.8
Ever regularly drank bottled water during pregnancy				
Yes	19.8	16.9	19.3	17.4
No	54.7	63.3	55.3	63.3
Unknown	25.5	19.8	25.4	19.3
Ever regularly took hot or very hot showers during pregnancy				
Yes	65.3	66.5	64.0	68.8
No	20.7	24.2	21.4	23.3
Unknown	14.1	9.3	14.6	7.9
Ever showered for >70 minutes per week during pregnancy				
Yes	19.7	22.7	19.0	24.2
No	61.9	64.0	62.1	63.9
Unknown	18.4	13.3	18.9	11.8

Table 4
Crude, Simple and Adjusted GEE Results Exposure Analyses for During Prenatal Period

Outcome	Exposure Group	Prenatal Period ^b	N - Yes	N - No	N - Total	Crude OR	Simple GEE OR	Multivariate GEE OR ^a
Diagnosis of ADD	None		62	756	818	-	-	-
	Low		69	626	695	1.3 (0.9,1.9)	1.4 (1.0,2.0)	1.4 (0.9,2.0)
Diagnosis of HD	High		42	480	522	1.1 (0.7,1.6)	1.1 (0.7,1.6)	1.0 (0.7,1.6)
	None		25	802	827	-	-	-
Tutoring for reading	Low		33	667	700	1.6 (0.9,2.7)	1.7 (1.0,2.9)	1.5 (0.9,2.7)
	High		13	516	529	0.8 (0.4,1.6)	0.8 (0.4,1.7)	0.8 (0.4,1.6)
Tutoring for math	None		130	701	831	-	-	-
	Low		116	582	698	1.1 (0.8,1.4)	1.1 (0.8,1.4)	1.1 (0.8,1.4)
Special class placement	High		92	437	529	1.1 (0.8,1.5)	1.1 (0.8,1.5)	1.1 (0.8,1.5)
	None		118	710	828	-	-	-
Individual education plan	Low		106	584	690	1.1 (0.8,1.5)	1.1 (0.8,1.5)	1.1 (0.8,1.5)
	High		78	450	528	1.0 (0.8,1.4)	1.0 (0.8,1.4)	1.0 (0.8,1.4)
Repeated a grade	None		98	731	829	-	-	-
	Low		98	592	690	1.2 (0.9,1.7)	1.3 (1.0,1.8)	1.3 (0.9,1.7)
High school graduate or less	High		54	469	523	0.9 (0.6,1.2)	0.9 (0.6,1.3)	0.8 (0.6,1.2)
	None		113	704	817	-	-	-
Adjusted for maternal age, race, and education, child's sex, and prematurity and/or low birth weight.	Low		109	583	692	1.2 (0.9,1.5)	1.2 (0.9,1.6)	1.2 (0.9,1.6)
	High		79	446	525	1.1 (0.8,1.5)	1.1 (0.8,1.5)	1.1 (0.8,1.5)
Cumulative prenatal exposure was designated low for a dose of PCE <10 g and high if the dose was >10 g over the nine months of gestation.	None		100	714	814	-	-	-
	Low		86	596	682	1.0 (0.8,1.4)	1.0 (0.8,1.4)	1.0 (0.7,1.4)
	High		69	447	516	1.1 (0.8,1.5)	1.1 (0.8,1.5)	1.1 (0.8,1.5)
	None		171	650	821	-	-	-
	Low		178	518	696	1.3 (1.0,1.7)	1.3 (1.0,1.7)	1.3 (1.0,1.7)
	High		114	408	522	1.1 (0.8,1.4)	1.1 (0.8,1.4)	1.0 (0.8,1.4)

^a Adjusted for maternal age, race, and education, child's sex, and prematurity and/or low birth weight.

^b Cumulative prenatal exposure was designated low for a dose of PCE <10 g and high if the dose was >10 g over the nine months of gestation.

Table 5
Crude, Simple and Adjusted GEE Results Exposure Analyses for Postnatal Period

Outcome	Exposure Group - Postnatal Period ^b	N - Yes	N - No	N - Total	Crude OR	Simple GEE OR	Multivariate GEE OR ^a
Diagnosis of ADD	None	56	682	738	-	-	-
	Low	88	834	922	1.3 (0.9,1.8)	1.3 (0.9,1.9)	1.3 (0.9,1.9)
Diagnosis of HD	High	29	346	375	1.0 (0.6,1.6)	1.1 (0.7,1.7)	1.0 (0.6,1.7)
	None	22	723	745	-	-	-
Tutoring for reading	Low	41	892	933	1.5 (0.9,2.6)	1.6 (0.9,2.8)	1.4 (0.8,2.5)
	High	8	370	378	0.7 (0.3,1.6)	0.8 (0.3,1.7)	0.7 (0.3,1.6)
Tutoring for math	None	117	633	750	-	-	-
	Low	174	757	931	1.2 (1.0,1.6)	1.3 (1.0,1.6)	1.2 (1.0,1.6)
Special class placement	High	47	330	377	0.8 (0.5,1.1)	0.8 (0.5,1.1)	0.8 (0.5,1.1)
	None	107	639	746	-	-	-
Individual education plan	Low	153	770	923	1.2 (0.9,1.6)	1.2 (0.9,1.6)	1.2 (0.9,1.6)
	High	42	335	377	0.7 (0.5,1.1)	0.8 (0.5,1.1)	0.7 (0.5,1.1)
Repeated a grade	None	87	660	747	-	-	-
	Low	130	791	921	1.2 (0.9,1.7)	1.3 (1.0,1.7)	1.2 (0.9,1.7)
High school graduate or less	High	33	341	374	0.7 (0.5,1.1)	0.7 (0.5,1.1)	0.7 (0.5,1.1)
	None	99	640	739	-	-	-
Adjusted for maternal age, race, and education, child's sex, and prematurity and/or low birth weight	Low	158	764	922	1.3 (1.0,1.8)	1.4 (1.0,1.8)	1.3 (1.0,1.8)
	High	44	329	373	0.9 (0.6,1.3)	0.9 (0.6,1.3)	0.8 (0.6,1.2)
Cumulative prenatal exposure was designated low for a dose of PCE <66.7 g and high if the dose was >66.7 g over the nine months of gestation.	None	98	633	731	-	-	-
	Low	122	791	913	1.0 (0.7,1.3)	1.0 (0.8,1.3)	0.9 (0.7,1.3)
	High	35	333	368	0.7 (0.5,1.0)	0.7 (0.4,1.0)	0.6 (0.4,1.0)
	None	155	588	743	-	-	-
	Low	226	700	926	1.2 (1.0,1.5)	1.2 (1.0,1.5)	1.1 (0.9,1.5)
	High	82	288	370	1.1 (0.8,1.5)	1.1 (0.8,1.4)	1.0 (0.7,1.4)

^a Adjusted for maternal age, race, and education, child's sex, and prematurity and/or low birth weight

^b Cumulative prenatal exposure was designated low for a dose of PCE <66.7 g and high if the dose was >66.7 g over the nine months of gestation.