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ORIGINAL RESEARCH

# Long-term Neurotoxic Effects of Early-life Exposure to Tetrachloroethylene-contaminated Drinking Water

Ann Aschengrau, ScD, Patricia A. Janulewicz, DSc, Roberta F. White, PhD, Veronica M. Vieira, DSc, Lisa G. Gallagher, DSc, Kelly D. Getz, PhD, Thomas F. Webster, DSc, David M. Ozonoff, MD, MPH
*Boston, Massachusetts; and Philadelphia, Pennsylvania*

**Abstract**

**BACKGROUND** Tetrachloroethene (PCE) is a common environmental and occupational contaminant and an acknowledged neurotoxicant. From 1968 through 1983, widespread contamination of public drinking water supplies with PCE occurred in the Cape Cod region of Massachusetts. The source of the contamination was a vinyl liner applied to the inner surface of water distribution pipes.

**OBJECTIVES** A retrospective cohort study (the Cape Cod Health Study) was undertaken to examine possible health consequences of early-life exposure to PCE-contaminated drinking water. This review describes the study methods and findings regarding the effects of prenatal and childhood exposure on neurologic outcomes during early adulthood, including vision, neuropsychological functioning, brain structure, risky behaviors, and mental illness. The review also describes the strengths and challenges of conducting population-based epidemiologic research in this unique setting.

**METHODS** Participants were identified by cross-matching birth certificates and water system data. Information on health outcomes and confounding variables was collected from self-administered surveys (n = 1689), neuropsychological tests (n = 63), vision examinations (n = 63), and magnetic resonance imaging (n = 42). Early-life exposure to PCE was estimated using a leaching and transport model. The data analysis compared the occurrence of each health outcome among individuals with prenatal and early childhood PCE exposure to unexposed individuals while considering the effect of confounding variables.

**FINDINGS** The study found evidence that early-life exposure to PCE-contaminated drinking water has long-term neurotoxic effects. The strongest associations were seen with illicit drug use, bipolar disorder, and post-traumatic stress disorder. Key strengths of the study were availability of historical data on affected water systems, a relatively high exposure prevalence and wide range of exposure levels, and little confounding. Challenges arose mainly from the historical nature of the exposure assessments.

**CONCLUSIONS** The Cape Cod Health Study demonstrates how scientists can take advantage of unique "natural experiments" to learn about the health effects of environmental pollution. This body of work has improved our understanding of the long-term health effects of early-life exposure to this common environmental contaminant and will help risk assessors and policymakers ensure that drinking water supplies in the United States are safe for vulnerable populations.

**KEY WORDS** brain, drinking water, tetrachloroethylene, vulnerable populations



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From the Department of Epidemiology, Boston University School of Public Health, Boston, MA (AA, LGG); Department of Environmental Health, Boston University School of Public Health, Boston, MA (PAJ, RFW, VMV, TFW, DMO); and the Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA 19104 (KDG). Address correspondence to A.A. (aaschen@bu.edu).

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## INTRODUCTION

Tetrachloroethene (also called tetrachloroethylene, perchloroethylene, perc, or PCE) is a widely used solvent in dry cleaning, textile processing, and metal degreasing.[1] In the United States, approximately 1.5 million people are occupationally exposed each year.[2] Most use is in small, inadequately controlled work settings such as dry cleaning, automobile repair, and machine shops, making PCE a common drinking water contaminant from improper management and disposal.[1] US surveys of drinking water contaminants have found it in 11% of tested wells[3] and 38% of surface water supplies.[4] Thus, it is not surprising that detectable levels of PCE in biologic media were found in 77% of a general US population sample.[5]

Although the typical source for drinking water contamination with PCE is improper disposal, an unusual scenario for widespread contamination of drinking water supplies occurred in the Cape Cod region of Massachusetts. The interior surface of water mains produced between 1968 and 1980 contained a plastic liner intended to eliminate taste and odor problems plaguing asbestos-cement pipes carrying the very soft water in the Cape Cod region. The liner was sprayed as a slurry composed of vinyl resin (Piccotex,™ Johns-Manville Corporation, Denver, CO, USA) dissolved in PCE. Because PCE is volatile, it was assumed it would evaporate completely during the drying process.[6] However, water samples taken in 1980 by the Massachusetts Department of Environment Protection (DEP) revealed that a substantial amount of PCE had remained in the liner and was leaching into the public drinking water supplies.[6]

A survey of local water departments indicated that approximately 660 miles of vinyl-lined asbestos-cement pipes (VL/AC) had been installed in 91 Massachusetts cities and towns.[7] The largest portion was installed in the Cape Cod region due to substantial residential development. PCE levels found in water samples from affected pipes on Cape Cod ranged from 1.5 to 7750 μg/L (ppb), depending on the rate of water flow.[6]

Digging up and replacing the VL/AC pipes was prohibitively expensive, so a program of flushing and bleeding the water distribution system was instituted in the most problematic areas. The objective was to reduce PCE levels below 40 μg/L, the suggested no-response level at the time.[6] However, by the time these risk reduction measures were implemented, tens of thousands of residents had been drinking PCE-contaminated water for up to 15 years. Monitoring now ensures that levels remain below the current maximum contaminant level of 5 μg/L.[8]

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.[9] In response to concern 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.[10,11]

After completing the cancer case–control studies, we initiated a new round of data collection for a retrospective birth-cohort study (the Cape Cod Health Study) to examine a more comprehensive array of possible health consequences of PCE exposure, particularly exposure early in life. The Cape Cod Health Study initially assessed the short-term effects of prenatal exposure to PCE-contaminated drinking water on reproductive outcomes, including low birth weight (BW),[12] prematurity,[12] miscarriage,[13] stillbirth,[14] and congenital anomalies.[15] More recently, we extended the study to examine the long-term effects of both prenatal and childhood exposure on neurologic outcomes, including vision,[16] neuropsychological functioning,[17] brain structure,[18] risky behaviors,[19] and mental illness.[20] There is a dearth of information on long-term neurotoxic effects of early-life exposure despite well-established short-term effects among adults.[1] The purpose of this review is to describe the methods and findings from the Cape Cod Health Study as well as the strengths and challenges of conducting population-based epidemiologic research in this unique setting.

## METHODS

**Identification of Participants.** Individuals born between 1969 and 1983 to women who lived in 1 of 8 Cape Cod towns with some VL/AC water pipes (Fig. 1) were eligible for enrollment in the birth cohort.[19] Participants were identified as likely exposed or likely unexposed by cross-matching maternal address on birth certificates with information from local water companies on the location and installation year of the VL/AC pipes. We tentatively designated participants as "exposed" if their birth residence was either directly adjacent to a VL/AC pipe or adjacent to a pipe connected to a VL/AC pipe and the only possible water flow to the


**Figure 1.** **Cape Cod Region of Massachusetts with highlighted study towns.**

residence was through the VL/AC pipe. Individuals initially designated as "unexposed" were randomly selected from the remaining resident births during this period and frequency matched to "exposed" participants on month and year of birth.

To increase the sample size and assess childhood exposure, we identified any older siblings of "exposed" and "unexposed" individuals who were born in Massachusetts from 1969 to 1983 (n = 1202). All older siblings were initially judged to be "unexposed" at birth because they were born while the family resided at an apparently unaffected residence. However, the original designation of all individuals was considered provisional until more extensive exposure assessments, as described here, were completed.

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**Follow-up and Data Collection.** Starting with the address on the birth certificate, we traced individuals to obtain their current addresses and telephone numbers using the Internet and other resources.[19] Letters were sent to all successfully traced individuals in 2007-2008, describing the general purpose of the study and requesting that they complete a survey about risky behaviors such as alcoholic beverage consumption and illicit drug use; health outcomes including mental illnesses; confounding variables; and their residential history, from birth through 1990, including the street address and calendar years of residence for all Cape Cod addresses. The survey also gathered information on an individual's knowledge of the PCE water pollution and self-assessments of PCE exposure to evaluate the possibility of recall bias.

In all, 5040 individuals were selected for the study, including 1910 "exposed" and 1928 "unexposed" and 1202 older "unexposed" siblings. About 6.6% could not be located, 45.5% were located but never responded to numerous contact attempts, 3.7% refused to participate, and 2.2% were deceased, leaving 1689 participants who returned the questionnaire. Characteristics of participants and nonparticipants (including their initial PCE exposure status, age, race, BW, and gestational duration) were quite similar, suggesting that nonresponse did not result in selection bias.[19]

Eligible participants who completed the survey were invited to participate in a clinical study comprised of neuropsychological tests to evaluate visuospatial abilities, attention and executive function, short-term memory, motor skills, academic achievement, omnibus intelligence and mood; vision examinations to assess color discrimination and contrast sensitivity; and magnetic resonance imaging (MRI) to measure white and gray matter volumes and white matter hypointensities.[16-18] Prior studies among adults suggested that these outcomes might be affected by early-life exposure to solvents.[21-25] Sixty-three participants completed the vision examinations and neuropsychological tests, and 42 underwent the MRI.

**Geocoding Residential Addresses.** Approximately 95% of reported residential addresses on Cape Cod were geocoded to a latitude and longitude (ArcGIS 8.1, ESRI, Redlands, CA, USA) by a team member who was blind to the exposure and outcome status of the participant.[19] When possible, addresses were geocoded to a specific parcel (ie, plot of land). Addresses that could not be geocoded to a specific parcel were geocoded to the closest parcel by street number, the middle of the streets $<1$ mile long, or the intersection with the nearest cross-street for streets $\geq 1$ mile.

**PCE Exposure Assessment.** An initial exposure status was provisionally assigned to each participant by examining maps of the pipe distribution network surrounding the birth residence. We then used a leaching and transport model to determine the final exposure designation based on an estimated relative mass of PCE delivered to each residence from the prenatal period through the age of 5 years.[1] Changes in the water distribution systems in the 1990s prevented assessment of PCE exposure beyond age 5.

The leaching model was previously developed for our cancer studies.[11,26] The model approximates the amount of PCE entering the drinking water 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. The pipe's initial stock of PCE was estimated using its diameter, length, and average thickness. Laboratory experiments have suggested that the leaching process followed a simple exponential decay process with rate constant of 2.25 years.[6]

The PCE delivered to a household depends not only on how much is leached, but where it is subsequently transported by the water distribution system. The transport algorithm requires an evaluation of water flow rate and direction, which are functions of the pipe geometry and the number of water users. We incorporated the Webler and Brown leaching algorithm into the open source code of EPANET water distribution modeling software to estimate PCE transport throughout a town's entire distribution system. EPANET, which was developed by the US Environmental Protection Agency to help utilities devise water quality monitoring programs,[27] has been applied in several epidemiologic studies assessing health effects of drinking water contaminants.[28,29]

We used maps of participant residences and the distribution systems to create a diagram representing the water sources, pipe characteristics, and nodes, denoting points of water use along the pipe. Information on the locations, installation dates, and diameters of all VL/AC water pipes was obtained from local water departments and the Massachusetts DEP. Each residence was assigned to the closest node on the distribution system. We assumed that all land parcels represented water users, all water users in the network

drew the same amount of water, and water sources did not change over the study period. These assumptions were supported by observations that the study area was primarily comprised of residences, and the distribution system changed little between the 1960s and 1980s, except for adding water sources to accommodate population growth.

The combined leaching and transport model simulated the flow of water through each town's distribution system to estimate the annual mass of PCE distributed to each node and all residences connected to the node. We assumed that residences served by a private well or located in towns with no VL/AC pipes had no PCE exposure at that address. We considered this reasonable because available records indicated little or no PCE contamination of these water sources.

Exposure during the prenatal period was estimated by multiplying the annual mass of PCE that entered the participant's residence during their birth year by 9/12. We estimated exposure during early childhood by summing the estimated mass of PCE that entered their residences from the month and year after birth through the month and year of the fifth birthday. Simple proportions were used to estimate exposure during partial years. Poor recall of bottle water use and bathing practices during pregnancy and childhood precluded incorporating these behavioral data into the exposure calculations.[19] These factors were also shown to have little effect on the exposure distribution in a prior cancer study.[30]

**Data Analysis.** The analysis compared the occurrence of each outcome among individuals with prenatal and early childhood PCE exposure to unexposed individuals. We examined the effects of any PCE exposure and, whenever possible, we assessed dose–response relationships according to exposure level. We were unable to study the separate effects of prenatal exposure alone because nearly all participants with prenatal exposure also had childhood exposure. We were unable to examine the effects of exposure only during childhood because there were too few participants in this category to provide stable results.

Risk ratios (RRs) were used to estimate the strength of the association between PCE exposure and the occurrence of dichotomous outcomes (eg, any illicit drug use). Mean differences were used for assessing relationships with continuous outcomes (eg, color confusion index). Ninety-five percent confidence intervals (95% CI) and *P* values were used to measure the precision of the associations. Confounding variables considered for adjusted analyses included demographic characteristics, key risk factors for the behavioral and health outcomes under study, and nondrinking water sources of solvent exposure. Depending on the outcome, variables that changed the crude estimate by >10% to 30% were included in final multivariate models.

## RESULTS

**Participant Characteristics.** As shown in Table 1, the characteristics of modeled exposed and unexposed participants were comparable.[19] Cape Cod Health Study participants were predominantly female, white, college-educated, married or cohabitating, employed and were, on average, 29 years old when they completed the study questionnaires. Few participants had possible occupational exposure to solvents but many had potential exposure from hobbies.

**PCE Exposure Levels.** Cumulative PCE exposure levels from the prenatal period through age 5 years spanned several orders of magnitude, ranging from 11 mg to 4668 g.[19] Mean and median cumulative exposure levels were 142 and 34 g, respectively, reflecting a long upper tail to the distribution. When we converted our modeled PCE exposure estimates to annual point concentrations, we estimated that PCE concentrations in water entering the study homes ranged from <1 to 5197 μg/L, levels consistent with public water analyses during the study period.[6]

**Exposure Self-Assessments.** Comparison of each participant's self-assessed exposure status to that derived from the modeled assessment revealed very few participants who knew their exposure status: 7% of participants considered exposed by the modeled assessment thought their drinking water was polluted by PCE, whereas 29% of exposed individuals thought their water was not polluted; 64% were uncertain.[20] Similarly, 31% of participants considered unexposed by the modeled assessment thought that their drinking water was not polluted, whereas 5% thought that their drinking water was polluted; 63% were uncertain.

**Risky Behaviors.** We defined risky behavior to be smoking, consumption of alcoholic beverages, and illicit drug use. The occurrence of risky behaviors was more common among participants who were highly exposed during gestation and early childhood.[19] In particular, increases in the risk for

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**Table 1. Selected Characteristics of Participants in the Cape Cod Health Study**

| Characteristic | Both Prenatal and Early Childhood Exposure (n = 831) | | Unexposed (n = 547) | |
|---|---|---|---|---|
| | n | % | n | % |
| Age* (n, mean, SD) | 831 | 29.2 (3.6) | 547 | 29.6 (3.8) |
| Gender | | | | |
| Male | 331 | 39.8 | 216 | 39.5 |
| Female | 500 | 60.2 | 331 | 60.5 |
| % White race | 818 | 98.4 | 539 | 98.5 |
| Educational level* | | | | |
| High school graduate or less | 128 | 15.4 | 67 | 12.2 |
| Some college | 192 | 23.1 | 144 | 26.3 |
| Four-year college grad or higher | 510 | 61.4 | 335 | 61.2 |
| Missing | 1 | 0.1 | 1 | 0.2 |
| Work status* | | | | |
| Employed | 719 | 86.5 | 487 | 89.0 |
| Not employed | 92 | 11.1 | 54 | 9.9 |
| Missing | 20 | 2.4 | 6 | 1.1 |
| Marital status* | | | | |
| Single | 272 | 32.7 | 157 | 28.7 |
| Married or cohabitating | 536 | 64.5 | 371 | 67.8 |
| Other | 19 | 2.3 | 12 | 2.2 |
| Missing | 4 | 0.5 | 7 | 1.3 |
| History of work-related solvent exposure* | | | | |
| Yes | 123 | 14.8 | 71 | 13.0 |
| No | 687 | 82.7 | 461 | 84.3 |
| Missing | 21 | 2.5 | 15 | 2.7 |
| History hobby with solvent exposure* | | | | |
| Yes | 700 | 84.2 | 462 | 84.5 |
| No | 124 | 14.9 | 79 | 14.4 |
| Missing | 7 | 0.8 | 6 | 1.1 |
| Mother's age at participant's birth (n, mean [SD]) | 831 | 27.2 (4.7) | 547 | 27.5 (4.4) |
| Mother's educational level at participant's birth | | | | |
| High school graduate or less | 327 | 39.4 | 178 | 32.5 |
| Some college | 243 | 29.2 | 188 | 34.4 |
| Four-year college grad or higher | 260 | 31.3 | 180 | 32.9 |
| Missing | 1 | 0.1 | 1 | 0.2 |
| Mother received prenatal care during participant's gestation | | | | |
| Yes | 794 | 95.5 | 520 | 95.1 |
| No | 4 | 0.5 | 0 | 0.0 |
| Missing | 33 | 4.0 | 27 | 4.9 |

* At the time the questionnaire was completed by the participant.

initiating smoking at a younger age (RR, 1.4; 95% CI, 0.8-2.5) and heavy smoking (RR, 1.3; 95% CI, 0.9-2.0), drinking frequently as a teenager (RR, 1.6; 95% CI, 1.1-2.3), and drinking heavily in the past 30 days (RR, 1.3; 95% CI, 1.0-1.7) were reported by participants in the highest exposure tertile.

Highly exposed participants also had increases in the risk for using >1 major drug as a teenager and as an adult (RR for teen use, 1.6; 95% CI, 1.2-2.2; RR for adult use, 1.5; 95% CI, 1.2-1.9). Specific drugs for which elevated risks were observed included crack/cocaine, psychedelics/hallucinogens, club/designer drugs, Ritalin without a prescription, and heroin. Limiting the analyses to participants without prenatal exposure to maternal cigarette smoking, marijuana use, and alcohol consumption strengthened these associations.

**Mental Health.** We examined the occurrence of depression, bipolar disorder, post-traumatic stress disorder (PTSD), and schizophrenia in relation to the study population.[20] Participants with any exposure during gestation and early childhood had elevations in the risk for bipolar disorder (RR, 1.8; 95% CI, 0.9-1.4) and PTSD (RR, 1.5; 95% CI, 0.9-2.5) that were further increased among participants in the highest exposure tertile (RR, 2.7; 95% CI, 1.3-5.6 for bipolar disorder and RR, 1.7; 95% CI, 0.9-3.2 for PTSD). By contrast, the risk for depression was not associated with prenatal and childhood PCE exposure (RR, 1.1; 95% CI, 0.9-1.4). The occurrence of schizophrenia was too rare to produce reliable conclusions.

**Vision.** The 63 participants with early-life exposure whose vision was examined also had evidence of long-term subclinical visual dysfunction.[16] Participants exposed to high PCE levels exhibited lower contrast sensitivity at intermediate and high spatial frequencies compared with unexposed participants. Exposed participants also exhibited poorer color discrimination than unexposed participants (mean difference in Farnsworth Color Confusion Index = 0.05; $P = 0.04$). No differences in visual acuity were observed.

**Neuropsychological Testing.** Among participants who completed neuropsychological testing, there was no evidence of major decrements in neuropsychological performance in relation to early-life exposure to PCE.[17] There were modest associations between exposure and diminished performance on tasks that assessed visuospatial function (mean difference = −0.3; 95% CI, −0.6 to +0.1), motor functioning (eg, mean difference Neurobehavioral Evaluation System finger tapping = −1.8; 95% CI, −5.7 to +2.2), learning and memory (mean difference = −0.2; 95% CI, −0.6 to +0.1), and attention and executive function (mean difference = −0.2; 95% CI, −0.5 to +0.1).[17] No associations were seen for decrements in performance on tests of omnibus intelligence, academic achievement, or language.

**Structural Magnetic Resonance Imaging.** MRI studies were performed on 42 participants. Early-life exposure to PCE was not associated with alterations in the brain structures as seen in structural neuroimaging studies.[18] In particular, no statistically significant differences were observed between exposed and unexposed participants on measures of white and gray matter volumes and white matter hypointensities.

**Strengths and Limitations of Cape Cod Health Study.** Like John Snow's cholera investigation in 1854 London,[31] the Cape Cod Health Study demonstrates how scientists can take advantage of unique "natural experiments" to learn about the health effects of environmental pollution. The unusual circumstances that led to the contamination of the public water supplies on Cape Cod presented both strengths and challenges for carrying out our research.

Although there is now considerable evidence to support the designation of PCE as a probable or likely human carcinogen,[1,32,33] its cancer-causing potential was suspected in 1980 when the water contamination was first publicized.[34] Thus, the discovery that PCE was leaching into public water supplies prompted state and local authorities to conduct a thorough investigation of the extent of the contamination and to swiftly develop and implement a remediation plan. The comprehensive investigation resulted in an extensive repository of water system records without which the present research would have been impossible to conduct.

The widespread nature and irregular pattern of contamination were also fortuitous circumstances for this study. First, the high exposure prevalence made it feasible to identify a sufficient number 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 pipes and thus different exposures (Fig. 2), resulting in minimal confounding by participant characteristics (Table 1). This also meant that PCE exposures were not correlated with other environmental contaminants such as trihalomethanes. The diverse settings where VL/AC pipes were installed, for example, high-flow locations along main thoroughfares and low-flow areas such as dead-end streets, also led to a wide range of exposure levels, another serendipitous circumstance of this study. 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 confounding.

Nevertheless, conducting the Cape Cod Health Study also presented considerable challenges. These arose mainly from the historical nature of the exposure assessments. These assessments did not account for behavioral characteristics (which were poorly recalled), and necessitated many

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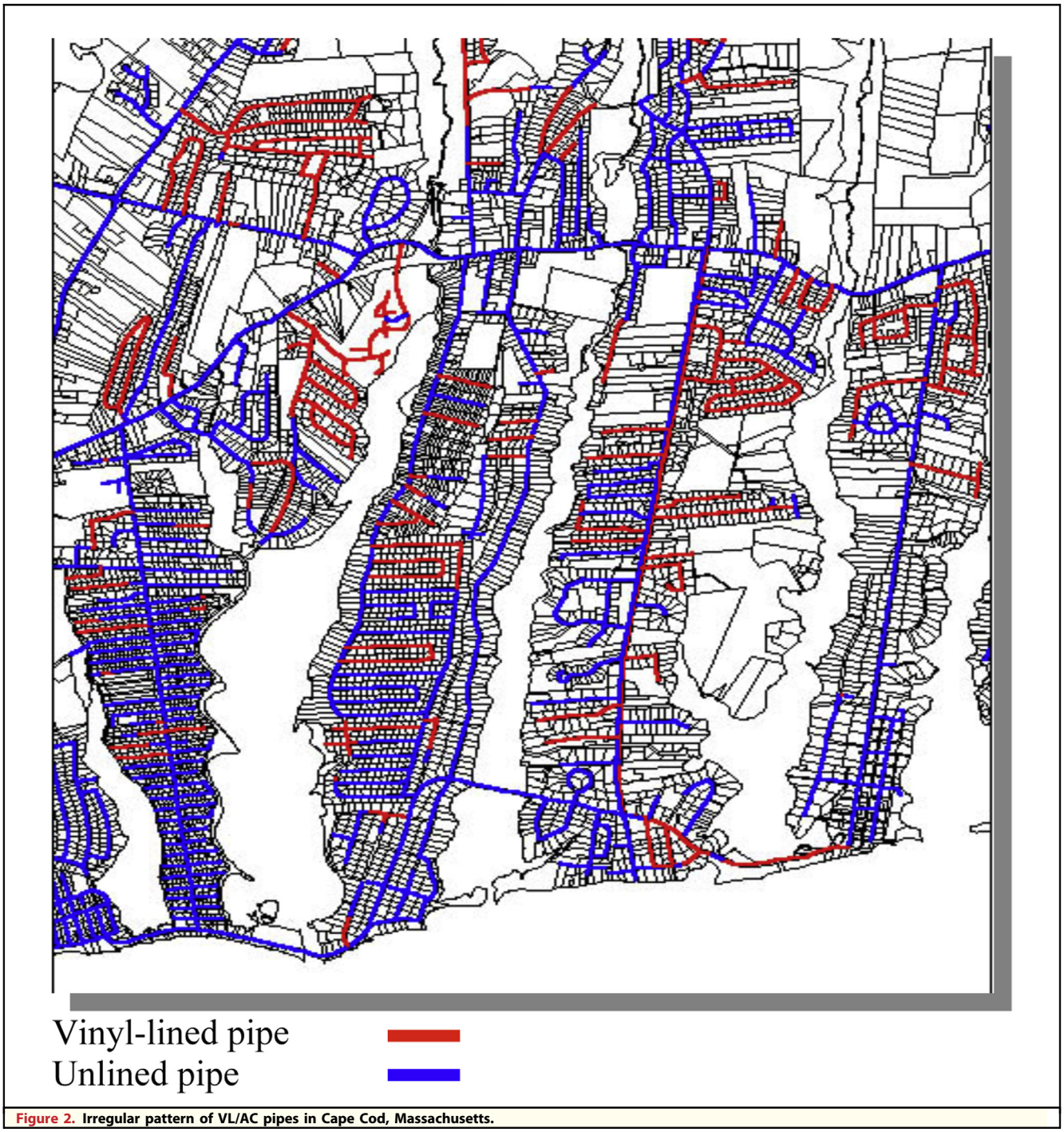


**Figure 2.** **Irregular pattern of VL/AC pipes in Cape Cod, Massachusetts.**

assumptions, both of which led to nondifferential exposure misclassification and likely attenuated the associations.

We were fortunate to locate a small number of drinking water sample test results from 1980 for comparison with our modeled exposure assessments. Although these historical samples were not completely satisfactory as a "gold standard" because they were only 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 ($\rho = 0.65$; $P < 0.00010$),[35] bolstering our confidence in the validity of our

assessments and suggesting that the extent of exposure misclassification may be relatively modest.

## CONCLUSIONS

PCE is a widespread environmental and occupational contaminant,[1,2] a probable carcinogen,[32,33] and an acknowledged neurotoxicant in the workplace setting.[32,33] Until now, few studies have shown noncancer effects at typical environmental exposure levels. An unusual scenario that resulted in PCE contamination of the drinking water in the Cape Cod region of Massachusetts afforded a unique opportunity to examine long-term neurotoxic effects of prenatal and early childhood exposures to PCE.

Results from the Cape Cod Health Study to date provide evidence that early-life exposure to PCE-contaminated drinking water has long-term neurotoxic effects (Table 2). Moderate associations were seen with illicit drug use, bipolar disorder, and PTSD. Additionally, modest associations were observed between early-life exposure and subsequent risky behaviors such as cigarette smoking and consumption of alcoholic beverages; diminished performance on tests of visuospatial function, learning and memory, attention and executive functioning, motor speed and mood; and subclinical decrements in color vision and contrast sensitivity. In contrast, no evidence of an association was seen for depression; diminished performance on tests of omnibus intelligence, academic achievement, and language; visual acuity; and alterations in brain structure as seen on neuroimaging. Because the study population is highly educated and predominantly white, these results may not be generalizable to more ethnically diverse and disadvantaged populations.

Although the Cape Cod Health Study is the first to report these long-term neurotoxic effects, the results are concordant with many other investigations of shorter-term neurologic effects among adults and children following solvent exposure.[1] The mode of action by which PCE may cause neurotoxicity is unknown. However, this small fat-soluble molecule easily crosses the blood–brain barrier and has high affinity for the lipophilic tissues of the brain. Additionally, experimental evidence suggests several possible mechanisms, including peroxidation of cell membrane lipids,[36] loss of myelin,[37] fatty acid changes in the brain,[38] and interference with neurotransmitters and γ-aminobutyric acid$_A$ receptors.[39] Because PCE is a common environmental contaminant, it is important to understand its long-term effects on the health of vulnerable populations such as pregnant women and their developing fetuses. This body of work has taken an important step toward improving understanding of the long-term neurotoxic effects of early-life exposure to PCE and will help risk assessors and policymakers ensure that US drinking water supplies are safe for all to consume.

**Table 2. Summary Long-term Neurotoxic Effects of Early-Life Exposure to Tetrachloroethylene-contaminated Drinking Water in the Cape Cod Health Study Population**

| Health/Test Outcome | Strength of Association |
|---|---|
| Risky behaviors | |
| Cigarette smoking | + |
| Alcoholic beverage consumption | + |
| Illicit drug use | ++ |
| Mental illness | |
| Depression | 0 |
| Bipolar disorder | ++ |
| Post-traumatic stress disorder | ++ |
| Vision tests | |
| Visual acuity | 0 |
| Contrast sensitivity | + |
| Color vision | + |
| Neuropsychological tests | |
| Omnibus intelligence | 0 |
| Academic achievement | 0 |
| Language | 0 |
| Visuospatial function | + |
| Learning and memory | + |
| Attention and executive functioning | + |
| Motor speed | + |
| Mood | + |
| Brain structure according to magnetic resonance imaging | |
| White matter volume | 0 |
| Gray matter volume | 0 |
| White matter hypointensities | 0 |

+, Modest association (eg, RRs ranging from 1.3 to 1.4); ++, moderate association (eg, RRs ranging from 1.4 to 2.1); 0, no association (eg, RRs ranging from 1.0 to 1.1).

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