

# Exhibit 216

# Cancer Risk and Tetrachloroethylene-contaminated Drinking Water in Massachusetts

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**ABSTRACT.** A population-based case-control study was used to evaluate the relationship between cases of bladder cancer ( $n = 61$ ), kidney cancer ( $n = 35$ ), and leukemia ( $n = 34$ ) and exposure to tetrachloroethylene from public drinking water. Subjects were exposed to tetrachloroethylene when it leached from the plastic lining of drinking water distribution pipes. Relative delivered dose of tetrachloroethylene was estimated, using an algorithm that accounted for (1) residential history and duration, (2) whether lined pipe served the neighborhood, (3) distribution system flow characteristics, and (4) pipe age and dimensions. Whether or not latency was considered, an elevated relative risk of leukemia was observed among ever exposed subjects (adjusted OR = 1.96, 95% CI = 0.71–5.37, with latency; adjusted OR = 2.13, 95% CI = 0.88–5.19, without latency) that increased further among subjects whose exposure level was over the 90th percentile (adjusted OR = 5.84, 95% CI = 1.37–24.91, with latency; adjusted OR = 8.33, 95% CI = 1.53–45.29, without latency). When latency was ignored, there was also an increased relative risk of bladder cancer among subjects whose exposure level was over the 90th percentile (adjusted OR = 4.03, 95% CI = 0.65–25.10). Given that tetrachloroethylene is a common environmental and workplace contaminant in the United States, its carcinogenic potential is a matter of public health concern.

DURING THE LATE 1970s in six New England states, it was discovered that tetrachloroethylene (PCE) was leaching into drinking water from the inner vinyl lining of certain asbestos cement water distribution pipes.<sup>1</sup> The vinyl liner had been introduced in the late 1960s to solve taste problems associated with the action of ag-

gressive New England water on the pipes. The liner was applied to the inner surface of the pipe as a slurry of vinyl resin in the solvent PCE, which, because of its volatility, was assumed to disappear in the curing process. However, substantial quantities of PCE remained and slowly leached into the water.

Initial investigation in Massachusetts disclosed approximately 650 miles of vinyl-lined/asbestos cement (VL/AC) pipes throughout the state. A large proportion had been installed in the five towns of the Upper Cape Cod area (Barnstable, Bourne, Falmouth, Mashpee, and Sandwich).<sup>1</sup> Typical concentrations in affected lines in one town (Falmouth) ranged from 1 600–7 750 µg/l at low-use (dead-end) sites to 1.5–80 µg/l at medium- and high-use sites.<sup>2</sup> The Massachusetts Department of Environmental Protection instituted a regular schedule of flushing and continuous bleeding to lower the levels below 40 µg/l, based on the then existing U.S. Environmental Protection Agency (EPA) Suggested No Adverse Response Level (SNARL) of 20 µg/l, adjusted for pipe aging and exposure time. However, by the time these risk management practices were initiated, thousands of residents had already been drinking PCE-contaminated water, some for as many as 10 y.

In 1985, several years after the PCE contamination was discovered, the Massachusetts Department of Public Health reported elevations in cancer mortality in the Upper Cape Cod area for the period from 1969 through 1983, compared with state-wide averages.<sup>3</sup> In particular, consistently elevated mortality rates were seen for lung cancer and leukemia.<sup>4</sup> Moreover, with the inception of the Massachusetts Cancer Registry in 1982, statistically significant excesses were seen in the annual incidence rate of cancers of the breast, colon/rectum, lung, and blood-forming organs, and statistically unstable increases were seen for cancers of the pancreas, kidney, and bladder in the Upper Cape region, compared with state-wide averages.<sup>5</sup>

Numerous other known or suspected environmental hazards also affected the Upper Cape region, among them water and air contamination from the Massachusetts Military Reservation (including Otis Air Force Base). Several groundwater plumes contaminated with fuels, solvents, and other chemicals were emanating from the Military Reservation and other locations. Most public water supplies had only low levels of volatile organic chemicals (less than 3 ppb), including trihalomethanes, benzene, trichloroethylene, dichloroethylene, and dichloroethane, whereas the sole chlorinated surface water supply had very modest trihalomethane levels (the highest concentration of chloroform detected was 13 ppb). Three wells of one groundwater supply showed some evidence of solvent contamination (the highest TCA level detected was 35 ppb). No vinyl chloride contamination was detected.

In response to substantial concern by organized elements of the general public, we undertook a set of population-based case-control studies to evaluate the relationship between nine types of cancer (lung, breast, colorectal, bladder, kidney, pancreas, brain, and liver cancer, and leukemia) and a number of environmental exposures. Exposure to PCE from the public drinking water distribution systems was examined in relation to only three of these cancers—bladder cancer, kidney cancer, and leukemia—because prior occupational studies had suggested an association with these cancers and because limited resources did not permit evaluation of all nine cancer sites.<sup>6–13</sup>

## Methods

**Selection and enrollment of study population.** The cases were incident cancers of the bladder ( $n = 79$ ), kidney ( $n = 42$ ), and leukemia ( $n = 44$ ) diagnosed from 1983 through 1986 among permanent residents of the five Upper Cape towns and reported to the Massachusetts Cancer Registry. Even though cases diagnosed during an additional year (1982) were available for inclusion, budgetary constraints did not allow their use. Comparison with cancer incidence rates from the nearby Connecticut Cancer Registry and from the American Cancer Society indicates that the Massachusetts Registry has nearly complete reporting for the cancer sites and geographic area under study.<sup>14</sup>

Controls were selected to represent the population that gave rise to the cases, characterized as demographically similar permanent residents of the same towns during the period 1983–1986. Inasmuch as many cases were elderly and deceased at the start of the study, three sources were used to identify comparable controls efficiently: (1) Living controls under 65 y were selected, using random digit dialing; (2) those aged 65 y and over were selected randomly from lists of Medicare beneficiaries provided by the Health Care Financing Administration; and (3) deceased controls of similar ages were selected randomly from death certificates of Upper Cape residents who had died subsequent to 1983.

**Living controls under age 65.** Random digit dialing selected a random sample of living telephone subscribers under 65 y of age who resided in the five Upper Cape towns during the case ascertainment period. According to the 1980 Census, more than 95% of housing units in Massachusetts had telephone service. A total of 2 236 residential households were identified (Table 1). Of this total, 62.7% did not have any members who met the eligibility criteria. Another 20.4% never answered the phone after numerous calls, and 5.8% refused to answer the screening questions that determined eligibility. Ultimately, 249 households were identified with an eligible respondent.

**Living controls aged 65 and over.** Random digit dialing is not an efficient technique for identifying elderly individuals, and so living controls aged 65 y and over

**Table 1.—Selection and Enrollment of Random Digit Dial Controls**

	Number
Households called	2 236
Exclusions	
Never reached any household member	456
Reached household but no eligible respondent	1 402
Reached household but respondent refused screening questions	129
Eligible respondent identified	249
Eligible respondent refused interview, never able to contact, too ill, language barrier	65
Interviewed	184

were identified, using lists of the elderly provided by the Health Care Financing Administration (HCFA). It is estimated that HCFA has a 95% enumeration of individuals 65 y of age and older in the United States.<sup>15</sup> A total of 611 HCFA controls were selected randomly from the population of the five Upper Cape towns, using a sampling scheme that stratified on age and gender. The vital status and residence of HCFA controls during the case ascertainment period were determined before interview, and all deceased individuals and non-Upper Cape residents were excluded.

**Deceased controls.** Controls who died between January 1, 1983 and December 3, 1989 were selected randomly from a listing of all deaths occurring among residents of the five Upper Cape towns provided by the Massachusetts Department of Vital Statistics and Research. All individuals, regardless of cause of death, were eligible for inclusion. A total of 918 deceased controls were selected, using a scheme that stratified on age, gender, and year of death. Prior to interview, the deceased control's residence during the case ascertainment period was determined, and all nonresidents were excluded.

**Follow-up and interviews.** Current addresses and telephone numbers of subjects or their next-of-kin were identified from Cancer Registry and HCFA records; state Resident's Lists; Registry of Motor Vehicles drivers' license records; Department of Vital Statistics' death, birth, and marriage records; physicians; tumor registrars; telephone books; and directory assistance. In accordance with Cancer Registry guidelines, permission was first sought from treating physicians before interviewing living cases.

Trained personnel carried out structured interviews, either over the telephone (86%) or in-person (14%), to obtain a 40-y residential history; information on demographic characteristics; confounding variables, such as smoking, relevant medical and occupation history, including exposure to PCE, benzene, and other solvents; bottled water consumption; and usual bathing habits. Usual bathing habits were determined by asking subjects if they took mostly showers, mostly baths, or showers and baths about equally, when at home. The questionnaire was pretested and substantially used in its original form.

Job titles and industries were coded, using a modification of the Standard Industrial Classification (1987) and Standard Occupational Classification (1990) manuals.<sup>16,17</sup> Occupational exposure to PCE and related solvents was assessed, using a combination of direct questions and industry and job title information.

Overall, 80.6% of the cases, 75.9% of HCFA controls, 78.8% of dead controls, and 73.9% of eligible random digit dial controls were interviewed (Tables 1 and 2). Interview rates were similar for the three cancer sites: 79.7% for bladder cancer, 83.3% for kidney cancer, and 79.5% for leukemia. The demographic characteristics among interviewed and noninterviewed subjects were quite similar. Among noninterviewed cases, 56.3% were male, 100% were white, 62.5% were aged 60 y and older, and 50.0% were alive at interview; among noninterviewed HCFA and dead controls, 41.2% were male, 94.7% were white, 89.5% were aged 60 y and older, and 43.5% were alive at interview. No information was available on noninterviewed random digit dial controls.

Three site-specific control groups were selected for analysis: first, by stratifying each case group on the basis of age (in decades), gender, vital status, and if dead, year of death, and then by selecting all controls who fell into a stratum with at least one case. This sampling scheme resulted in a large number of controls being selected for each cancer site (911 for bladder cancer, 856 for kidney cancer, and 820 for leukemia). There was considerable overlap between control groups.

Next, an index year was selected for each control group that was comparable to the diagnosis date for the cases. In this method, only exposures of control subjects that occurred before the index year were counted. The median diagnosis year of the case group was used as the index year for its control group because that year was likely to be closest to the diagnosis year. Controls who first moved to the Upper Cape after the index year, cases and controls with incomplete residential histories, and one control with no PCE data were excluded. There remained 61 bladder cancer cases and 852 controls; 35 kidney cancer cases and 777 controls; and 34 leukemia cases, including chronic lymphocytic ( $n = 10$ ), acute lymphocytic ( $n = 4$ ), chronic myelogenous ( $n = 3$ ), acute nonlymphocytic

**Table 2.—Selection and Enrollment of Cases, Health Care Financing Administration (HCFA), and Dead Controls**

	No. of cases			No. of controls	
	Bladder cancer	Kidney cancer	Leukemia	HCFA*	Dead
Selected	79	42	44	611	918
Exclusions					
Never found or contacted	7	6	4	21	97
Not eligible	0	0	2	53	27
M.D. or subject refusal	9	1	3	73	71
Total excluded	16	7	9	147	195
Interviewed	63	35	35	464	723

\*Selected randomly from lists provided by the Health Care Financing Administration (HCFA).

(n = 11), and other unspecified leukemia (n = 6), and 737 controls for the final analysis.

**PCE exposure estimation.** Relative exposure to PCE in drinking water was estimated, using an algorithm developed by Webler and Brown.<sup>18</sup> The relative delivered dose (RDD) was defined as the estimated mass of PCE in milligrams that entered a given house as a solute in drinking water over a specified time period. Webler and Brown used the word "relative" to emphasize that the number was an estimate, rather than an accurate determination.

The algorithm used to estimate RDD is based on a model for PCE leaching from vinyl-lined pipe proposed and tested by Demond.<sup>2</sup> A number of assumptions are made in the model: (1) the finite amount of PCE in the plastic lining is distributed uniformly on the inside surface of the pipe, (2) the amount of PCE per unit length was the same for all pipes at the time of installation and did not change over time, (3) PCE leaching is far from equilibrium because water is always flowing, and (4) the leaching rate decreases with time as aging decreases the diffusion coefficient for PCE within the plastic matrix.

The initial stock of PCE in a pipe is directly proportional to the interior surface area of the pipe, given by the pipe's diameter and length. The rate at which this initial stock leaches may depend on numerous other factors, including the physical parameters of the pipe; water temperature, density, and viscosity; and the water flow rate. In the Webler-Brown model, a pipe's initial stock of PCE is estimated from its length and diameter, and the leaching rate is estimated by the water flow and pipe age.

The flow rate is affected by the distribution network geometry and the load on the network. The effects of network geometry were simplified by considering four generic cases: (1) dead-ends, (2) circles, (3) circles with taps, and (4) in-line. Any specific case was considered to be one of these geometries or a combination of them. The load on the pipes at any time depends on the number of hoses connected to it, the date of connection, and the water consumption of each house. Tax assessment and water distribution system maps were used to determine the spacing of house connections. Water flow was assumed to be unidirectional, and all houses were assumed to draw the same quantity of water continuously during the subject's entire residency.

In order to implement Webler and Brown's model, the location of the VL/AC pipes in all public water supply systems in the area was determined. Five of the 11 water suppliers reported no VL/AC pipes in their districts. The remaining 6 supplies provided water distribution maps that showed the location of the VL/AC pipes and their installation dates.

Next, all subjects' residences on VL/AC streets since 1967 (the first year VL/AC pipes were installed in the area) were identified and located on the distribution network. A schematic diagram was drawn for every residence on a VL/AC street, and on each diagram the water flow to the residence was depicted. Each schematic also indicated the following key model variables:

location and number of loads, pipe length(s), and installation date(s).

Creation of the schematic frequently involved judgment of water distribution characteristics not provided by the water supply maps. Water flow direction was determined by examining various features of the distribution network, including water source locations and pipe sizes, whereas determining the load distribution required judging the point where residences connected to the water mains. A strict protocol was devised so that all decisions were made consistently. All exposure assessments were conducted without knowing who was a case or control.

**Data analysis.** The crude (unadjusted) analysis examined PCE exposure in relation to each cancer site. Exposure was examined as a dichotomous "ever" versus "never" variable or as unexposed, "low," and "high" relative delivered doses (RDDs). We defined "low" RDD as a level up through the 90th percentile among the exposed, and "high" RDD was defined as a level above 90th percentile among the exposed. The RDD frequency distribution among all exposed controls combined was used to determine the 90th percentile. This cut point consolidated the most highly exposed individuals who were in the uppermost tail of the exposure distribution.

Individuals were considered exposed if they had at least one exposed residence during the relevant time period. If an individual had more than one exposed residence, RDDs were cumulated over all residences. The referent category always consisted of unexposed subjects.

Analyses were conducted with and without taking the latent period for cancer into account. When latency was taken into account, only exposures that occurred prior to the latent period were counted, whereas when latency was not accounted for, exposures that occurred up until the time of the diagnosis or index year were counted. The latent period used was 5 y for leukemia and 15 y for bladder and kidney cancer.<sup>19,20</sup>

The exposure odds ratio was used to estimate the strength of the relationship (relative risk) between PCE exposure and the cancer site. Odds ratios were calculated for each cancer site only if there were at least two exposed cases. The small number of cases did not permit calculation of the odds ratios for age and histologic subcategories. The potential modifying effects of drinking bottled water and bathing habits were examined in stratified analyses. Confidence intervals (95% CI) were calculated, using Fisher's exact method,<sup>21</sup> in order to assess the statistical significance of the crude associations.

Multiple logistic regression was used to control simultaneously for potential confounding variables.<sup>22</sup> The antilog of the beta coefficient of the exposure variable served as an estimate of the odds ratio. Adjusted analyses were performed only if there were at least two exposed cases. Sex; age at diagnosis or index year; vital status at interview; educational level; and occupational exposure to PCE, benzene, and other solvents were controlled in all adjusted analyses. In addition, other well-known strong risk factors for each cancer site were controlled if they occurred with reasonable frequency in the population. Our rule of thumb was that at least

three cases had to have a positive history of the potential confounder for it to be controlled. Prior medical treatment with irradiation was included in the leukemia analysis; usual number of cigarettes smoked and history of a urinary tract infection or stone were included in the kidney cancer analysis; and usual number of cigarettes smoked, history of a urinary tract infection or stone, and history of a cancer-associated job (rubber, cable, and dye manufacturing and leather work) were included in the bladder cancer analysis.<sup>23,24</sup> The 95% confidence intervals for the adjusted odds ratios were

calculated, using the maximum likelihood estimates of the standard errors.<sup>25</sup>

## Results

Overall, the cases and controls were predominantly white, elderly, currently married or widowed, and Catholic or Protestant (Table 3). A larger proportion of leukemia and bladder and kidney cancer cases than controls had less than 12 y of education. A larger proportion of bladder and kidney cancer cases than con-

**Table 3.—Distribution (%) of Demographic and Other Characteristics of Cases and Controls**

Characteristic	Bladder cancer cases (n = 61)	Bladder cancer controls (n = 852)	Kidney cancer cases (n = 35)	Kidney cancer controls (n = 777)	Leukemia cases (n = 34)	Leukemia controls (n = 737)
Gender						
Male	73.8	52.7	65.7	48.3	47.1	47.1
Female	26.2	47.3	34.3	51.7	52.9	52.9
Race						
White	98.4	96.6	94.3	96.9	97.1	96.2
Other	1.6	3.4	5.7	3.1	2.9	3.8
Age at diagnosis or index year (y)						
1-49	0.0	1.4	2.9	1.3	17.7	4.6
50-59	9.8	10.1	8.6	7.1	2.9	6.5
60-69	42.6	39.9	28.6	42.5	20.6	35.6
70-79	36.1	33.9	51.4	39.8	32.4	37.3
80+	11.5	14.8	8.6	9.4	26.5	16.0
Marital status						
Married	72.1	66.9	57.1	64.6	58.8	58.6
Widowed	24.6	23.3	31.4	25.0	26.5	28.0
Other*	3.3	9.9	11.4	10.4	14.7	13.5
Religion						
Catholic	55.0	45.9	45.7	45.7	45.5	47.9
Protestant	41.7	47.6	54.3	48.2	51.5	47.2
Jewish	0.0	2.7	0.0	3.0	0.0	2.9
Other	3.3	3.8	0.0	3.1	3.0	2.1
Education level (y)						
Less than 12	31.6	18.5	20.6	16.8	30.3	19.9
12	24.6	32.6	32.4	35.0	33.3	35.8
13-15	14.0	24.6	20.6	25.5	15.2	23.2
16 or more	29.8	24.3	26.5	22.6	21.2	21.1
Ever regular cigarette smoker	88.5	66.5	74.3	66.7	64.7	68.5
Ever had occupational exposure to solvents†	34.4	26.2	25.7	25.2	35.3	25.3
Ever regularly drank bottled water	11.9	9.3	5.9	9.4	11.8	9.0
Usual bathing habits						
Mostly showers	62.7	51.3	51.4	51.0	48.5	47.7
Mostly baths	27.1	30.9	34.3	32.0	33.3	34.4
About equal	10.2	17.8	14.3	17.1	18.2	18.0
History of urinary tract infection	52.5	22.5	37.1	24.2	—‡	—‡
History of urinary tract stones	15.3	8.3	19.4	8.8	—‡	—‡
Prior medical treatment with radiation	—‡	—‡	—‡	—‡	8.8	14.9
Alive at interview	65.6	57.0	51.4	61.5	23.5	34.6

\*Includes never married, separated, and divorced.  
†Based on answers to direct questions regarding exposure to perchloroethylene, tetrachloroethylene, trichloroethylene, benzene, gasoline, kerosene, paint thinners, and other solvents; and industry and job title information.  
‡Not a risk factor for this cancer site.

trols were male, whereas leukemia cases and controls were most equally divided between the sexes. Both bladder and kidney cancer cases reported smoking cigarettes and a history of urinary tract infections or stones more often than did their controls. Cigarette smoking did not vary substantially among leukemia cases and controls, but prior medical treatment with radiation was more common among the controls. More bladder and leukemia cases than controls were classified as having occupational solvent exposure; this exposure, however, was equally common among the kidney cancer cases and controls. A small and similar proportion of the three case and control groups reported drinking bottled water regularly prior to the diagnosis or index year. The usual bathing habits of kidney cancer and leukemia cases and controls prior to the diagnosis or index year were similar, whereas bladder cancer cases were more likely than controls to report taking mostly showers. Finally, the majority of bladder and kidney cancer cases and controls were alive at interview; however, most leukemia cases and controls were deceased.

A total of 5.7% of all subjects combined were classified as being ever exposed to PCE when latency was taken into account; 13.5% were so classified when latency was ignored. Relative delivered dose (RDD) estimates obtained from the Weblor-Brown model ranged from 0.01 to 90.6 mg with latency and from 0.01 to 209.4 mg without latency; the 90th percentiles among exposed controls were 27.1 and 44.1 mg, respectively.

Six cases (5 leukemia and 1 bladder cancer) were considered ever exposed when the latent period was considered (Table 4). There was a 1.72-fold increase in the crude relative risk of leukemia among ever exposed subjects (95% CI = 0.50–4.71) that increased to 5.78 among exposed subjects whose RDD was above the 90th percentile (95% CI = 0.98–22.97). The relative

risks were 1.96 (95% CI = 0.71–5.37) and 5.84 (95% CI = 1.37–24.91), respectively, after adjusting for confounding.

Thirteen bladder cancer, 6 kidney cancer, and 7 leukemia cases were considered ever exposed to PCE when the latent period was ignored. The crude relative risks were 1.55 (95% CI = 0.74–3.01), 1.23 (95% CI = 0.40–3.11), and 1.77 (95% CI = 0.63–4.33), respectively, among these ever exposed subjects. Again, the crude relative risk of leukemia increased more among subjects with "high" RDDs (OR = 5.95; 95% CI = 0.58–31.72). The crude relative risk of bladder cancer also increased among subjects with "high" RDDs (OR = 6.04; 95% CI = 1.32–21.84). No kidney cancer cases were considered exposed to "high" RDDs.

Most risk estimates, if calculated without considering latency, changed only slightly when confounders were controlled with multiple logistic regression techniques. The adjusted relative risks among ever exposed subjects were 1.39 for bladder cancer (95% CI = 0.67–2.91), 1.08 for kidney cancer (95% CI = 0.42–2.79), and 2.13 for leukemia (95% CI = 0.88–5.19). However, the adjusted relative risks among subjects whose RDD was above the 90th percentile decreased to 4.03 (95% CI = 0.65–25.10) for bladder cancer and increased to 8.33 (95% CI = 1.53–45.29) for leukemia.

Given that only a very few subjects reported that they drank bottled water regularly, we were, therefore, unable to describe the relationship between PCE exposure and cancer occurrence among these subjects. However, the relative risks were quite similar when the analysis was restricted to subjects who never drank bottled water regularly.

With respect to the examination of usual bathing habits, the crude relative risks of leukemia and kidney cancer were increased among subjects with any PCE exposure

**Table 4.—History of PCE Exposure among Cases and Controls (With and Without Considering Latency), Crude Odds Ratios, and 95% Confidence Intervals**

	PCE exposure history			Crude odds ratio (95% CI)		
	Any	Low*	High*	Any	Low*	High*
<b>With latency†</b>						
<b>Bladder cancer</b>						
Cases (n = 61)	1	0	1	—	—	—
Controls (n = 852)	7	0	7	—	—	—
<b>Kidney cancer</b>						
Cases (n = 35)	0	0	0	—	—	—
Controls (n = 777)	3	0	3	—	—	—
<b>Leukemia</b>						
Cases (n = 34)	5	2	3	1.72	0.84	5.78
Controls (n = 737)	67	55	12	(0.50–4.71)	(0.09–3.48)	(0.98–22.97)
<b>Without latency</b>						
<b>Bladder cancer</b>						
Cases (n = 61)	13	9	4	1.55	1.16	6.04
Controls (n = 852)	127	117	10	(0.74–3.01)	(0.48–2.48)	(1.32–21.84)
<b>Kidney cancer</b>						
Cases (n = 35)	6	6	0	1.23	1.36	—
Controls (n = 777)	112	101	11	(0.40–3.11)	(0.45–3.45)	—
<b>Leukemia</b>						
Cases (n = 34)	7	5	2	1.77	1.38	5.95
Controls (n = 737)	94	86	8	(0.63–4.33)	(0.40–3.78)	(0.58–31.72)

who reported taking mostly baths. The crude relative risks of leukemia were 4.73 (95% CI = 0.73–21.81) with latency and 5.03 (95% CI = 0.99–21.25) without latency, and the adjusted relative risks were 4.89 (95% CI = 0.96–24.93) and 7.02 (95% CI = 1.50–32.79), respectively. The crude and adjusted relative risks of kidney cancer were 2.91 (95% CI = 0.47–12.62) and 3.23 (95% CI = 0.54–19.17), respectively, without latency.

Whereas the crude relative risk of bladder cancer among subjects with any PCE exposure did not change appreciably with respect to subjects' bathing habits (OR = 1.47, 95% CI = 0.25–5.74 for mostly baths; OR = 1.84, 95% CI = 0.75–4.13 for mostly showers), when confounders were controlled, the relative risk of bladder cancer was further increased among subjects who took mostly baths (OR = 1.99; 95% CI = 0.40–10.01).

No associations were seen between bladder and kidney cancer and leukemia and the other drinking water contaminants investigated. None of the cases lived within the groundwater plume delineations when latency was considered, and only one leukemia case lived there when latency was ignored. Furthermore, no increases in risk were observed among subjects who ever had a residence served by either the chlorinated surface water supply with modest trihalomethane levels or the groundwater supply with evidence of solvent contamination.

## Discussion

In this study, we found that exposure to PCE-contaminated drinking water was associated with an increased risk of leukemia, whether or not the latent period was taken into account. Furthermore, there was evidence that the increased leukemia risk was dose related. Because of small numbers, the relative risk of bladder cancer could not be estimated when the latent period was considered; however, when latency was ignored, an increased relative risk was present that also appeared to be dose related. No kidney cancer cases were considered exposed when latency was taken into account, and no meaningful increases in the risk of kidney cancer were detected without latency.

We hypothesized that taking mostly showers (versus mostly baths) would further increase the relative risks because both inhalation and dermal absorption during showers result in greater exposure levels than does the primarily dermal absorption during baths.<sup>26</sup> However, subjects who took mostly baths appeared to have had additional increases in the relative risks of leukemia, bladder, and kidney cancer.

Many estimates of association did not achieve the traditional level of statistical stability (95% confidence interval did not include 1.0), but the size of the case groups was small. Given that the exposures occurred many years ago, it is impossible to know with absolute certainty the precise PCE levels to which subjects were exposed. Our exposure estimate was based on the Weblor-Brown model. Any false model assumptions or errors determining the model input variables would have led to errors in estimating the RDDs. Even if water concentration of PCE were estimated accurately, sub-

jects consume and come into contact with varying amounts of water at home, depending upon personal circumstances. Thus, it is likely that risk estimates from this study are biased downward because of nondifferential errors in exposure estimation.

Furthermore, the use of average latent periods (15 y for the solid tumors and 5 y for leukemia) for analyses that considered exposures as cancer initiators also contributes to nondifferential exposure misclassification. Inasmuch as individual latent periods will certainly vary from those estimates, some relevant exposures may have been missed, and other nonrelevant ones may have been included in the analyses with latency. Whereas exposure estimation was conducted without knowing who was a case or a control, and given that the latent period adjustments were the same for cases and controls these errors were as likely to occur for the cases as the controls and also bias the results toward the null.

It is unlikely that the results observed in this study can be accounted for by confounding, observation, or selection bias. With respect to confounding, sex, age, vital status at interview, educational level, occupational exposure to PCE, benzene, and other solvents, and other well-known cancer risk factors that occurred with reasonable frequency were controlled in the multivariate analysis. Residual confounding by uncontrolled factors, including other drinking water contaminants such as benzene and trihalomethanes, drugs, and infectious agents, remains a possible but unlikely explanation for the results. These risk factors would need to be related strongly to risk, tightly correlated with PCE exposure, and sufficiently common to have produced the large odds ratios observed in our study. As regards the other drinking water contaminants, no vinyl chloride and very low levels of benzene were detected in the public water supplies. Trihalomethane levels were also generally low because only 1 of the 11 public water suppliers treated water with chlorine. The sole chlorinated water supply had modest trihalomethane levels, the highest level of chloroform detected being 13 ppb. No associations were seen between the three cancers under study and exposure to either the chlorinated surface water supply or the groundwater supply with evidence of solvent contamination.

Given the nature of the questionnaire and the interview setting, it was not possible to blind the interviewers to the disease status of the respondent. However, because the interview was highly structured, the questions written carefully, and the interviewers well-trained and experienced, the possibility of systematic differences in soliciting, recording, or interpreting information was minimized. In an effort to help achieve comparable quality of the interview data, deceased controls were included who had proxy interviews in the same fashion as deceased ones. In addition, recall bias was not an issue because the PCE exposure estimates were conducted independently of the interview.

Selection bias arising through differential surveillance, diagnosis, and referral of individuals was also unlikely because the cancer cases were obtained from all incident cases from the Massachusetts Cancer Registry.

Comparison with other sources indicates nearly complete reporting for the cancer sites and geographic area under study. Selection bias stemming from nonresponse related to both the disease and exposure was also not likely given that the follow-up and interview rates were fairly high and similar among cases and controls, and the demographic characteristics of participants and nonparticipants were alike.

There are several lines of evidence to support the carcinogenicity of PCE and similar chemicals. Vinyl chloride (monochloroethylene), the first in the series of chlorinated ethylenes to which PCE belongs, is a known human carcinogen, and PCE, like di- and trichloroethylene, is considered by EPA and IARC to be a probable human carcinogen (EPA class B2, IARC class 2B). Whereas PCE has given equivocal (though largely negative) results in short-term tests,<sup>27-29</sup> PCE, given by gavage to B6C3F1 mice, produced hepatocellular carcinomas in both male and female animals.<sup>30</sup> Results for gavaged rats could not be interpreted because of high morbidity and mortality to the animals. However, a subsequent bioassay conducted by the National Toxicology Program with inhalation exposures resulted in increased mononuclear cell leukemia, and a dose-related trend for renal tubular adenomas and adenocarcinomas in rats and confirmed an increase in hepatocellular carcinomas in mice.<sup>31</sup> Both the EPA and IARC classifications of PCE as a probable human carcinogen depend largely on these animal bioassay results.

The available epidemiologic evidence is consistent with toxicological evidence of PCE's carcinogenicity.<sup>6-11</sup> Much of the evidence originates from studies of the dry cleaning industry, where PCE was the predominant solvent from the 1960s.<sup>12,13</sup> As a result of the original NCI bioassay, NIOSH examined a cohort of 1 597 subjects employed prior to 1960 in dry cleaning shops where PCE was the primary solvent.<sup>6</sup> Difficulty with follow up limited conclusions, but results suggested that cancer of the colon may have been associated with occupational exposure in this cohort (SMRs: 182 for whites and 187 for blacks; 11 observed deaths, 6.98 expected among whites, 6.77 expected among blacks). Urinary tract cancer also seemed to be increased. Additional analyses conducted 5 y later<sup>7</sup> found continued significant mortality excesses from urinary tract (12 observed versus 4.7 expected) and cervical cancer (assumed to be confounded by the generally low socioeconomic status of these workers). There were also excesses in intestinal cancer in each of the four independent union cohorts examined. The majority of these workers could also have been exposed to petroleum solvents, however, and examination of a subcohort of 615 PCE-only workers did not find significant mortality excesses, although information on latency is not provided.

Proportional mortality ratio (PMR) analyses of 330 deceased members of a dry cleaners union found an excess of lung and cervical cancer and slight excesses of leukemia and liver cancer.<sup>8</sup> Subsequent follow up of more than 5 000 union members found significant excesses for esophageal cancer (SMR = 210; 13 observed, 6.1 expected) and statistically unstable excesses for laryngeal cancer (SMR = 160; 3 observed, 1.9 ex-

pected), lung cancer (SMR = 130; 47 observed, 37.1 expected), bladder cancer (SMR = 170; 8 observed, 4.8 expected), thyroid cancer (SMR = 330; 3 observed, 0.9 expected), lymphosarcoma (SMR = 170; 7 observed, 4.2 expected) and Hodgkin's disease (SMR = 210; 4 observed, 1.9 expected).<sup>9</sup> Risk for hematopoietic and lymphatic cancer was increased four-fold in workers whose jobs involved the heaviest exposure.

Other epidemiological studies have also implicated PCE as a carcinogen. Katz and Jowett conducted a proportional mortality study of dry cleaning and laundry workers, using Wisconsin death certificates, and found elevated PMRs for cancers of the kidney (PMR = 257; 7 observed, 2.7 expected), cervix (PMR = 195; 10 observed, 5.1 expected) and genitals, unspecified (PMR = 495; 4 observed, 0.8 expected), and smaller excesses for cancers of the bladders (PMR = 189; 5 observed, 2.6 expected), skin (PMR = 207; 4 observed, 1.9 expected) and lymphosarcoma (PMR = 170; 6 observed, 3.4 expected).<sup>10</sup> Similarly, Duh and Asal found an excess proportion of kidney cancers in a study of 440 Oklahoma death certificates on which "laundry worker" was listed as the usual occupation.<sup>11</sup> A case-control study of pancreatic cancer by Lin and Kessler found an association with occupational exposure to dry cleaning and gasoline (RR = 5.1 for those exposed more than 10 y, with clear dose-response trend for duration of exposure).<sup>32</sup> Collectively, these studies have suggested associations of dry cleaning work with leukemia, cancer of the urinary tract, cervix, lung, colon, pancreas, and liver.

In addition, other studies have associated use of solvents, included PCE, with various forms of cancer. A study of a leukemia cluster in Woburn, Massachusetts, was linked to access to well water contaminated with TCE and PCE.<sup>33</sup> Whereas questions have been raised about this study by some,<sup>34-38</sup> the results are consistent with both animal studies and other epidemiological work.

In conclusion, we have found evidence for an association between PCE-contaminated public drinking water and leukemia and bladder cancer. In some EPA surveys, 14 to 26% of groundwater and 38% of surface water sources have some degree of PCE contamination. Thus, its carcinogenic potential is a matter of significant public health concern.<sup>29</sup>

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Preliminary analyses of these data were reported to the Massachusetts Department of Public Health in September 1981 (Aschengrau and Ozonoff 1991). The results in the current paper differ from those given in that report because of minor corrections in the final study population, adjustment for additional confounding variables, and a correction in the method of cut point determination for the exposure. The study questionnaire is available upon request.

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