

Exhibit 234

Drinking Water Contamination and the Incidence of Leukemia and Non-Hodgkin's Lymphoma

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A study of drinking water contamination and leukemia and non-Hodgkin's lymphoma (NHL) incidence (1979–1987) was conducted in a 75-town study area. Comparing incidence in towns in the highest trichloroethylene (TCE) stratum ($>5 \mu\text{g/l}$) to towns without detectable TCE yielded an age-adjusted rate ratio (RR) for total leukemia among females of 1.43 (95% CI 1.07–1.90). For females under 20 years old, the RR for acute lymphocytic leukemia was 3.26 (95% CI 1.27–8.15). Elevated RRs were observed for chronic myelogenous leukemia among females and for chronic lymphocytic leukemia among males and females. NHL incidence among women was also associated with the highest TCE stratum (RR = 1.36; 95% CI 1.08–1.70). For diffuse large cell NHL and non-Burkitt's high-grade NHL among females, the RRs were 1.66 (95% CI 1.07–2.59) and 3.17 (95% CI 1.23–8.18), respectively, and 1.59 (95% CI 1.04–2.43) and 1.92 (95% CI 0.54–6.81), respectively, among males. Perchloroethylene (PCE) was associated with incidence of non-Burkitt's high-grade NHL among females, but collinearity with TCE made it difficult to assess relative influences. The results suggest a link between TCE/PCE and leukemia/ NHL incidence. However, the conclusions are limited by potential misclassification of exposure due to lack of individual information on long-term residence, water consumption, and inhalation of volatilized compounds. *Key words:* drinking water, leukemia, lymphoma, perchloroethylene, trichloroethylene. *Environ Health Perspect* 102:556–561 (1994).

Since the mid-1970s, several epidemiologic studies have suggested an association between organic drinking water contaminants, especially chlorinated volatile compounds, and increased cancer incidence. In Woburn, Massachusetts, exposures to the solvents trichloroethylene (TCE) and perchloroethylene (PCE) were linked to a leukemia cluster, primarily acute lymphocytic leukemia among children (1), while another recent study in Massachusetts observed an association between leukemia and PCE (2).

The New Jersey Department of Health previously conducted an exploratory study of leukemia incidence in a part of the state with a broad range of drinking water contamination. Analysis of data from the New Jersey State Cancer Registry and from the first rounds of mandatory water testing in 1984–1985 demonstrated a statistically significant association of the concentrations of TCE and PCE with the overall

leukemia rate (1979–1984) among females residing in a 27-town study area (3).

The current investigation expands the geographic scope of that earlier study to 75 towns, examines disease incidence between 1979 and 1987, and includes non-Hodgkin's lymphomas (NHL) as well as leukemias. As with the earlier study, interviews were not conducted. The hypotheses were: 1) that the incidence of leukemia is associated with exposure to TCE and/or PCE; 2) that childhood leukemia, in particular, is associated with TCE and/or PCE; 3) that NHL is associated with TCE and/or PCE; and 4) that sex may be an effect modifier. These hypotheses were drawn from the previous findings in New Jersey and Woburn, Massachusetts, and upon the similar cellular origin of lymphoid cells in certain histologic groupings of NHL and leukemias (4,5).

Methods

Study Population

The study area encompassed 75 municipalities with a 1980 population of almost 1.5 million in four counties (Bergen, Essex, Morris, and Passaic), including the 27 towns in three counties used in the original study. As in the original study, the 48 added municipalities were selected because they were in a portion of the state that was 95% served by monitored public water supplies and was primarily urban and residential so that town coding in the New Jersey State Cancer Registry (NJSCR) is likely to be accurate (i.e., rural route numbers and postal boxes are not complicating factors). The study area did not exhibit major population influx during the 1970–1980 period (as reported in the 1980 U.S. Census). Municipalities were included only if more than 80% of the population was served by a public water supply.

Finally, the study area was selected to ensure a variety of exposure situations (uncontaminated and contaminated with various substances), each with a population size large enough to enable sufficient statistical power for observing associations between exposures and incidence of leukemias and NHL.

Disease Measurement

Incident cases of primary leukemias and NHL from 1979 to 1987 were obtained from the NJSCR. The NJSCR is popula-

tion-based and reporting is mandatory by law. However, case ascertainment was augmented by death certificates. Ascertainment including death certificates is estimated to be greater than 99% complete during this period. All New Jersey hospitals cooperate or permit inspection of records. Registries in New York, Pennsylvania, and Delaware provide data on New Jersey residents diagnosed in those states. Information from the NJSCR includes age at diagnosis, sex, race, town of residence at diagnosis, and histologic type according to the World Health Organization International Classification of Diseases for Oncology (6). Leukemias were grouped as acute or chronic and by lymphocytic or myelogenous histologic type. The NHL were grouped as low, intermediate, or high grade, encompassing groups A–C, D–G and H–J, respectively, from the working formulation proposed by the National Cancer Institute (7) and the International Classification of Diseases for Oncology Field Trial Edition (8). The diffuse large cell/reticulosarcoma group of the intermediate-grade NHL were examined separately because of the separate analysis of reticulosarcomas in some older occupational studies and because of evidence that the survival rate in this grouping resembles that of the high-grade group (9). High-grade NHL was also examined without Burkitt's lymphoma because of the possible viral etiology of the latter (10). Mucocutaneous lymphomas were grouped separately but included with total NHL.

Death certificates accounted for 15% of the leukemia and 8% of the NHL ascertainment. Except as noted in the Results section, cases ascertained only by death certificate were not included in the analysis because 1) 90% of the NHL cases ascertained from death certificates alone did not have specific histology, 2) information was lacking on whether a case was primary or secondary, and 3) it was not possible to ensure correct municipal coding, especially for older individuals constituting the majority of death certificate cases.

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Exposure Assessment

In 1984, New Jersey enacted the landmark amendments to the State Safe Drinking Water legislation requiring all public community water systems to monitor semiannually for 14 volatile organic compounds (VOCs), including many chlorinated solvents. Since 1981, water supplies serving more than 10,000 persons have also been tested for water chlorination by-products, the trihalomethanes (THMs). In 1984–1985 (the first rounds of mandatory testing), the most commonly occurring non-THM VOCs were TCE, PCE, and 1,1,1-trichloroethane (11). Sources may include improper disposal by commercial and individual users, as well as groundwater pollution from hazardous waste sites.

The exposure data were derived from the 1984–1985 measurements of 4 THMs and 14 other VOCs in the mandatory monitoring program administered by New Jersey Department of Environmental Protection and Energy for public water supplies and from historical monitoring data conducted in 1978–1984 by New Jersey Department of Environmental Protection and Energy and New Jersey Department of Health. The New Jersey Department of Environmental Protection and Energy and the purveyors also provided details on the distribution system size, well or surface water use, patterns of water purchases among systems, and significant changes in water supply and use for 1970–1985. Water supply changes largely consisted of closings of contaminated wells during the 1980–1985 period. That groundwater was typically replaced by surface water from adjacent systems. Reports from 1986–1988 were also examined for any evidence of contamination which could have been missed during the 1984–1985 testing.

For the exposure estimates of the 1984–1985 data, we used an average derived from a previously generated month-to-month analysis conducted as part of a New Jersey Department of Health study on reproductive outcomes (12). This procedure differed from the earlier leukemia study (3). Each town required a separate method of summary estimation because of the idiosyncrasies of each distribution system and the varied space-time patterns of sampling (12). The average and maximum concentrations of THMs, total non-THM VOCs, TCE, and PCE were estimated by considering together samples of finished water from the plant and samples taken from the distribution system (i.e., from the tap at a site other than a treatment plant). Homogeneous mixing was a necessary and, for most systems, a reasonably valid simplification. The number of distribution system samples for each

supply varied from 2 to 50, depending upon the size of the supply and evidence of contamination. If water was also purchased in bulk from another system, the summary results were modified by amounts proportional to the estimated dilution factor, assuming complete mixing. Ultimately, a single summary average and maximum concentration for each contaminant was assigned to an entire municipality. Only results using the summary average are reported here because the relative ordering of municipalities by maximum levels was close to that of average concentrations.

Exposure variables were categorized for optimum use of the Poisson statistical methodology (see below). Four categories represented total VOC summary exposures for the 1984–1985 period: <0.1 (unexposed), 0.1–5, >5–20 and >20 ppb (with ppb equivalent to µg/l). The TCE and PCE summary exposure categories were each grouped as <0.1, 0.1–5, and >5 ppb. The latter cutpoint was chosen because the current U.S. EPA maximum contaminant levels for TCE and PCE were set at 5 ppb (13,14) and because it included a population of sufficient size to provide useful statistical power for the analyses. Total trihalomethanes were analyzed in four divisions with the highest category of >50 ppb. The highest assigned TCE level was 67 ppb, the highest assigned PCE level was 14 ppb, the highest assigned total non-THM VOC level was 92.9 ppb, and the highest assigned THM level was 87.6 ppb. The population-weighted average of TCE and PCE in the highest categories were 23.4 ppb and 7.7 ppb, respectively. Four of the six municipalities in the highest TCE category were also in the highest PCE stratum. There were 11 municipalities in the highest PCE stratum. The population-weighted concentrations of TCE and PCE in the highest strata of the 48 municipalities added for this expanded study are 8.7 and 10.5 in 2 and 4 added towns, respectively. The relative distribution of TCE and PCE contamination among the study towns is further described elsewhere (15).

Due to the low concentrations and small populations involved with the other non-THM contaminants, the power to detect increased incidence was limited. Therefore, analysis was limited to presence or nondetection of these other contaminants.

New Jersey Department of Environmental Protection and Energy and New Jersey Department of Health surveys of VOCs during the 1978–1983 period were used to provide corroborating evidence for the use of the 1984–1985 data on TCE and PCE as surrogates for contaminant concentrations during the 1970s. The 1984–1985 data were used as the primary

source of exposure estimation because the earlier surveys were usually collected in response to known contamination, and quality assurance and quality control were better during the mandatory monitoring period. The 1978–1983 data are further described elsewhere (15).

The detection limits in the early 1980s for TCE and PCE at the Department of Health Laboratories, the testing facility generating most of the study data prior to mandatory utility testing in 1985, were in the 0.5–2.0 ppb range, with coefficients of variation ranging from 5–15% at 5 ppb. The overall data in 1985 (including data submitted by utilities) was of similar or better quality. Misclassification of the 1984–1985 data should be low at levels greater than 5 ppb, particularly since many verification samples were taken from systems contaminated above the 5 ppb level.

Data Analysis

Log-linear regression with a Poisson distribution model (16) was used to generate incidence rate ratios (RR) and the 95% CI within the study area. Poisson regression fitted the age- and sex-specific count of cases in towns grouped by exposure strata, offset by the logarithm of the stratum-specific population. Analysis was performed by EGRET software (17), which provides coefficients of effect, RRs, and 95% CI relative to the lowest level of a variable (e.g., the group of towns with the lowest contamination level). Poisson regression of categorically approximated exposure does not require *a priori* assumptions about the shape of the dose response relating exposure to disease incidence.

The modeling strategy attempted to determine exposure RRs, adjusted for age, and included added terms to look at possible confounders and interaction. All models included age because of its significant association with incidence. Age was grouped into 0–19, 20–49 and 50–69, and 70+ years of age at diagnosis. Since the earlier NJDOH study (3) reported an association between leukemia and drinking water contaminants among females only, cases were grouped by sex for separate analysis.

Estimated carcinogenic air emissions tabulated on the municipality level from the 1987 Toxics Release Inventory (TRI) (18) were also analyzed for potential confounding or effect modification on the estimates for drinking water contaminants exhibiting significant association with leukemias or NHL. Compounds included known, probable, and possible carcinogens, using U.S. EPA terminology (19). The resulting categories of annual fugitive plus stack emissions for a municipality were: under 300 pounds, 300–2,999 pounds, 3,000–29,999 pounds and over

30,000 pounds. Specific ambient outdoor air data were not available on a municipality level.

Municipal socioeconomic measures, represented by average annual household income and percentage of high school graduates, were also analyzed. Towns were grouped into two categories: under \$20,000, \$20,000–24,999, \$25,000–29,999 and greater than \$30,000 average annual income; and under 65%, 65–74%, 75–84% and greater than 85% high school graduates.

Results

Case Description

During the nine-year span of 1979–1987, there were 1190 incident cases of leukemia (663 among males and 527 among females of all races in the 75 towns). Approximately 25% of the leukemias were not specified beyond acute/chronic or, alternatively, lymphoid/myeloid. The age-specific incidence rates for leukemias in the study area (including cases ascertained only by death certificates) were within 10% of the state rates.

There were 1658 incident cases of non-Hodgkin's lymphoma (NHL) (841 cases among males and 817 among females of all races). About 25% were not classified by specific histology. The majority of cases were low- and intermediate-grade NHL. The age-specific incidence rates (including death certificate ascertained cases) were within 10% of the state rates.

Because total leukemia and NHL incidence rates were similar between whites and nonwhites in the study area, all races were combined in the analyses presented here. Inclusion of New Jersey State Cancer Registry cases ascertained only by death certificates did not affect the results, except as noted below.

Total VOCs

A statistically significant association between leukemia incidence among females and residence in towns in the highest exposure stratum (>20 ppb) of total VOCs from the 1984–1985 monitoring period was observed. The age-adjusted RR of leukemia incidence among females, comparing the highest total VOC exposure category to the lowest (unexposed) exposure stratum, was 1.42 with a 95% CI of 1.05–1.90. Similarly, the RR for NHL among females in the highest exposure stratum was 1.24 (95% CI 0.97–1.57).

Trichloroethylene

For leukemias among females the age-adjusted RR of the highest TCE exposure stratum (>5 ppb) to the unexposed (none detected) stratum (Table 1) was statistically significantly elevated for total leukemias and for ALL. RRs for CLL and CML were

also elevated among females, but the 95% CI included 1.0. There was not a statistically significant association of total leukemias with TCE among males, but the RR for CLL was elevated.

Childhood leukemia among females, particularly ALL, was statistically elevated in the highest category of TCE exposure when compared to the unexposed stratum. Childhood ALL represented two-thirds of all ALL cases. The RR was 3.26 (95% CI 1.29–8.28) for females diagnosed with ALL before 20 years of age, based on 6 cases in the highest TCE exposure category (36 cases total). For females diagnosed before 5 years of age, the RR was 4.54 (95% CI 1.47–10.6), based on 5 cases. Among young males there were no significant associations.

Inclusion of cases ascertained by death certificates only affected the results for childhood leukemia. The RR was reduced to 2.41 (95% CI 0.98–5.92) for ALL among females in the highest TCE stratum diagnosed before age 20, while for females diagnosed before age 5 the RR was reduced to 3.78 (95% CI 1.22–8.81). When ana-

lyzed by combined 1978–1985 exposure data, the RR for all cases of female childhood ALL in the highest category of TCE exposure was 3.60 (95% CI 1.31–9.93).

The incidence rates of NHL among females (Table 2) were also more strongly associated with the higher levels of TCE than among males. The age-adjusted RR for total NHL among females in the highest TCE exposure stratum was statistically elevated. RRs among intermediate-grade NHL and high-grade NHL were statistically elevated among females in the highest TCE category. In these two groups, diffuse large cell/reticulosarcoma NHL, and non-Burkitt's high-grade NHL were most strongly associated.

Males also exhibited a statistically elevated RR for diffuse large cell/reticulosarcoma NHL and a nonsignificantly elevated rate for non-Burkitt's high-grade NHL in the highest TCE category.

In general, there was not much difference in the observed RRs with the inclusion of data from 1978–1983, such that the TCE variable represented all data from 1978–1985. While there was reduced

Table 1. Number of reported cases, age-adjusted rate ratios (RR), and 95% confidence interval (95% CI) for leukemias in the northern New Jersey study area, 1979–87, by trichloroethylene (TCE) exposure category and sex, all races

TCE exposure (ppb)	Cases		RR (95% CI)	
	Males	Females	Males	Females
Total leukemias				
<0.1	438	315	1.0	1.0
0.1–5.0	162	156	0.85 (0.71–1.02)	1.13 (0.93–1.37)
>5.0	63	56	1.10 (0.84–1.43)	1.43 (1.07–1.90)
Total	663	527		
Acute lymphocytic leukemia				
<0.1	45	25	1.0	1.0
0.1–5.0	16	22	0.91 (0.53–1.57)	1.85 (1.03–3.70)
>5.0	3	7	0.54 (0.17–1.70)	2.36 (1.03–5.45)
Total	64	54		
Chronic lymphocytic leukemia				
<0.1	125	91	1.0	1.0
0.1–5.0	55	40	1.01 (0.74–1.39)	0.99 (0.68–1.44)
>5.0	25	18	1.49 (0.97–2.30)	1.57 (0.95–2.60)
Total	205	149		
Acute myelogenous leukemia				
<0.1	103	74	1.0	1.0
0.1–5.0	37	40	0.83 (0.58–1.21)	1.23 (0.84–1.81)
>5.0	15	7	1.08 (0.63–1.86)	0.75 (0.35–1.63)
Total	155	121		
Chronic myelogenous leukemia				
<0.1	55	44	1.0	1.0
0.1–5.0	15	16	0.63 (0.36–1.11)	0.83 (0.47–1.48)
>5.0	6	10	0.82 (0.35–1.91)	1.79 (0.90–3.55)
Total	76	70		
Other specified leukemias				
<0.1	29	10	1.0	1.0
0.1–5.0	11	6	0.87 (0.44–1.75)	1.38 (0.50–3.81)
>5.0	4	1	1.04 (0.36–2.94)	0.76 (0.10–5.98)
Total	44	17		
Unspecified leukemias				
<0.1	81	71	1.0	1.0
0.1–5.0	28	32	0.79 (0.52–1.22)	1.02 (0.68–1.56)
>5.0	10	13	0.95 (0.49–1.84)	1.47 (0.81–2.66)
Total	119	116		

strength of association in the highest TCE category with diffuse large cell NHL among females, in contrast, the association of non-Burkitt's high-grade NHL among females with the highest TCE category was strengthened (RR=5.79; 95% CI 1.74–19.2).

The 48 municipalities that were added to make up the current study area of 75 towns were also analyzed separately. The strengths of association of leukemia and non-Hodgkin's lymphoma incidences with the highest TCE stratum were similar in the 48 added towns compared to the total 75 towns in the current study, though the 95% CI were much wider. No cases of childhood ALL occurred in the highest TCE stratum in the 48 towns (less than one case was expected), but diffuse large cell NHL among males and non-Burkitt's high-grade NHL exhibited much stronger association.

Perchloroethylene

Only high-grade NHL among females, with or without Burkitt's lymphomas, was statistically associated with the highest PCE exposure category (Tables 3 and 4) and was the only histologic grouping significantly associated with both TCE and PCE. It was difficult to separate the relative influences of TCE and PCE because of the degree of correlation ($r = 0.63$) be-

tween TCE and PCE levels in the 75 towns and the number of towns with high concentrations of both.

When analysis included 1978–1983 exposure data in addition to the 1984–1985 data, the association was not statistically significant. Non-Burkitt's high-grade NHL among females was nonsignificantly associated with PCE in the 48 towns added in the expanded study.

Other Contaminants

No association was detected between leukemia or NHL incidence and THMs or with other non-THM VOCs, such as benzene, 1,1,1-trichloroethane, carbon tetrachloride, and *trans*-1,2-dichloroethylene. Percentage of groundwater composition of the water supply was not by itself associated with the incidence of total leukemia or NHL.

Only one town in the highest TCE stratum and one town in the intermediate TCE stratum were also contaminated with benzene in the 1–2 ppb range. There was no association between acute myelogenous leukemia or other leukemias and benzene. The strength of association of TCE with the incidence of childhood ALL among females and with non-Burkitt's high-grade NHL among females was unaffected by including benzene in the regression model.

Gross alpha radiation levels in water

(which do not include radon) were also available. Average levels were all below 5 picocuries per liter, the current U.S. EPA standard. Gross alpha radiation (greater or less than 1 pCi/l, with about one-third of the population in the higher category) was not associated with the incidence of total leukemia or NHL.

Estimated TRI carcinogenic air release in the study area was, with one exception, not by itself associated with the incidence rate of NHL or leukemia in either sex. While non-Burkitt's high-grade NHL among females was significantly associated with TRI in an age/TCE-adjusted model (RR=2.78; 95% CI 1.01–7.65), in that model the observed association with TCE in water was increased (RR=4.72; 95% CI 1.61–13.8).

Socioeconomic Factors

There were no significant differences between municipalities in the different TCE or PCE strata, based on municipal average annual household income and educational background (percentage of high school graduates) from data in the 1980 U.S. Census. Neither leukemias nor NHLs were associated with categorized municipal average income or education.

Discussion

An initial investigation conducted by Fagliano et al. (3) observed an association between both TCE and PCE in drinking water and the incidence of leukemia among females in a 27-town study area. For the current investigation, the original study area was expanded to 75 municipalities in order to include a larger exposed and unexposed population over a longer time period in order to enhance the power to detect associations for specific histological groupings of leukemia and NHL.

Of particular importance were elevated RRs for childhood ALL among females and non-Burkitt's high-grade NHL among females in the highest stratum of TCE exposure. Notably, incidence of diffuse large cell NHL, which may be as aggressive as high-grade NHL (9), was also associated with TCE exposure. These same NHL types were also associated with TCE exposure among males. The highest stratum of PCE contamination in the 1984–1985 data was also associated with non-Burkitt's high-grade NHL among females, but because of collinearity of TCE and PCE contamination, it was difficult to assess the relative influence of each.

This study uses geographic data aggregated by exposure, but the exposure variables in this study come close to estimating the exposure of all the population in an exposure category, approximating a nonecologic crude analysis (20). However, this

Table 2. Number of reported cases, age-adjusted rate ratios (RR), and 95% confidence interval (95% CI) for non-Hodgkin's lymphoma (NHL) in the northern New Jersey study area, 1979–87, by trichloroethylene (TCE) exposure category and sex, all races

TCE exposure (ppb)	Cases		RR (95% CI)	
	Males	Females	Males	Females
Total NHL				
<0.1	491	504	1.0	1.0
0.1–5.0	272	226	1.28 (1.10–1.48)	1.02 (0.87–1.20)
>5.0	78	87	1.20 (0.94–1.52)	1.36 (1.08–1.70)
Total	841	817		
Low-grade NHL: total				
<0.1	130	119	1.0	1.0
0.1–5.0	77	67	1.36 (1.03–1.81)	1.29 (0.96–1.74)
>5.0	20	21	1.15 (0.72–1.84)	1.37 (0.86–2.18)
Total	227	207		
Intermediate-grade NHL: total				
<0.1	216	211	1.0	1.0
0.1–5.0	117	87	1.22 (0.98–1.53)	0.93 (0.73–1.20)
>5.0	38	39	1.30 (0.92–1.84)	1.46 (1.03–2.05)
Total	371	337		
Intermediate-grade NHL: diffuse large cell/reticulosarcoma				
<0.1	123	114	1.0	1.0
0.1–5.0	67	48	1.25 (0.93–1.69)	0.95 (0.68–1.34)
>5.0	26	24	1.59 (1.04–2.43)	1.66 (1.07–2.59)
Total	216	186		
High-grade NHL: total				
<0.1	18	20	1.0	1.0
0.1–5.0	12	9	1.54 (0.74–3.20)	1.04 (0.48–2.30)
>5.0	4	6	1.72 (0.58–5.08)	2.43 (0.97–6.05)
Total	34	35		
High-grade NHL: non-Burkitt's				
<0.1	12	15	1.0	1.0
0.1–5.0	9	6	1.73 (0.73–4.11)	0.92 (0.36–2.37)
>5.0	3	6	1.92 (0.54–6.81)	3.17 (1.23–8.18)
Total	24	27		

Table 3. Number of reported cases, age-adjusted rate ratios (RR), and 95% confidence interval (95% CI) for leukemias in the northern New Jersey study area, 1979–87, by perchloroethylene (PCE) exposure category and sex, all races

TCE exposure (ppb)	Cases		RR (95% CI)	
	Males	Females	Males	Females
Total leukemias				
0	433	317	1.0	1.0
0.1–5.0	150	127	0.90 (0.75–1.08)	1.05 (0.85–1.29)
>5.0	80	83	0.84 (0.66–1.06)	1.20 (0.94–1.52)
Total	663	527		
Acute lymphocytic leukemia				
0	46	24	1.0	1.0
0.1–5.0	10	21	0.55 (0.27–1.12)	1.89 (1.04–3.44)
>5.0	8	9	0.81 (0.38–1.72)	1.58 (0.74–3.36)
Total	64	54		
Chronic lymphocytic leukemia				
0	129	93	1.0	1.0
0.1–5.0	48	37	0.94 (0.68–1.32)	1.01 (0.69–1.48)
>5.0	28	19	0.98 (0.65–1.47)	0.93 (0.56–1.52)
Total	205	149		

study is susceptible to misclassification of exposure due to the lack of individual information on long-term residence and actual exposure, which varies according to the quantity of water consumed from the tap, use of home water filtration, and the amount of inhaled compounds volatilized during nondrinking uses, such as showering, laundering and dish washing. Notably, in this type of study nondifferential misclassification of a nonproportional variable, such as exposure to contaminants in drinking water, tends to reduce the observed effect (21).

Improvements in the current study over the previous New Jersey Department of Health study include an exposure database given an extensive quality control review in conjunction with other New Jersey Department of Health studies. In addition, this study also used nonsystematic drinking water survey data from 1978–1983 to identify and/or corroborate the presence of specific contaminants temporally more relevant to the dates of diagnosis. A 5- to 20-year latency period is believed to characterize adult leukemo- and lymphomagenesis by radiation and occupational exposure to chemicals (4,5). If childhood leukemias have shorter latency periods, the available exposure data may be even more germane.

Because the TRI data from 1987 (18) were available on a municipal level, these data were used as an exploratory tool, serving as a surrogate for occupational and environmental exposures to suspected carcinogenic substances in air. Including the TRI variable in the model did not affect the association of TCE in drinking water with leukemia and NHL. However, the TRI variable is probably temporally inappropriate, is based entirely on estimates reported by the regulated companies, and in the absence of dispersion modeling, may

not reflect air concentrations by town.

Well-known etiologic factors in leukemia and lymphoma include certain genetic traits, ionizing radiation, infectious agents, DNA-repair enzyme deficiencies, and certain chemicals (4,5,22–24). In particular, occupational exposures to benzene have been linked to leukemias, especially AML, and lymphomas (25–27). Chlorophenoxy herbicides have been linked by some to the incidence of NHL (28–29), but not by others (30). The relative risk of myelogenous leukemia among smokers is moderately elevated (31–34).

While it is possible that radiation, occupational exposures, smoking, genetic predisposition, or infectious agents are distributed differentially among the exposure strata in this study, they are not likely to be differentially distributed to an extent that would affect these findings. Socioeconomic

differences between TCE strata were small.

Benzene was found in the water supplies of one town in the highest combined TCE and PCE exposure categories. Although the concurrent presence of benzene in the water supplies may limit conclusions about the strength of association with TCE and PCE, there was little statistical support for the influence of benzene contamination. In addition, AML, the type of leukemia most often associated with benzene in occupational studies (25,26) was not associated with benzene contamination of drinking water in this study.

Occupational studies of TCE and PCE exposures have found inconsistently elevated rates for leukemias and lymphomas, as well as for malignancies of the urinary tract, uterine cervix, and other sites (35–39). However, most studies were small, had short follow-up times, and were based on mortality.

Inhaled PCE (about 300–350 mg/kg) significantly increased the percentage of young F344/N rats that develop a mononuclear cell leukemia which arises spontaneously in senescent rats of this strain (40). Laboratory studies of adult mice have demonstrated elevated hepatic carcinomas after exposure to TCE (41,42) or PCE (40). Based on the rodent studies, both TCE and PCE have been classified as probable human carcinogens by the state of New Jersey (43). Human cancer risk could involve different potencies and different organs or cell types from those in the rodent studies. The cancer potency slope based on the 95% upper bound of the linearized multistage cancer model predicts that an added cancer risk of 1 per 100,000 is associated with lifetime ingestion of water contaminated with about 10 ppb of TCE or PCE

Table 4. Number of reported cases, age-adjusted rate ratios (RR), and 95% confidence interval (95% CI) for non-Hodgkin's lymphomas (NHL) in the northern New Jersey study area, 1979–87, by perchloroethylene (PCE) exposure category and sex, all races

TCE exposure (ppb)	Cases		RR (95% CI)	
	Males	Females	Males	Females
Total NHL				
0	487	509	1.0	1.0
0.1–5.0	235	187	1.25 (1.07–1.46)	0.95 (0.81–1.13)
>5.0	119	121	1.10 (0.90–1.35)	1.08 (0.89–1.32)
Total	841	817		
Intermediate-grade NHL: diffuse large cell/reticulosarcoma				
0	129	116	1.0	1.0
0.1–5.0	61	39	1.23 (0.91–1.67)	0.86 (0.60–1.24)
>5.0	26	31	0.91 (0.60–1.39)	1.21 (0.82–1.80)
Total	216	186		
High-grade NHL: total				
0	23	19	1.0	1.0
0.1–5.0	9	5	1.11 (0.51–2.41)	0.71 (0.26–1.89)
>5.0	2	11	0.41 (0.09–1.76)	2.66 (1.27–5.60)
Total	34	35		
High-grade NHL: non-Burkitt's				
0	15	15	1.0	1.0
0.1–5.0	7	3	1.26 (0.51–3.09)	0.53 (0.15–1.82)
>5.0	2	9	0.61 (0.14–2.65)	2.74 (1.20–6.26)
Total	24	27		

(43). This predicted added risk is in the same range as the increased leukemia and NHL incidence rates observed in the highest TCE stratum in this study. The rodent bioassays have been criticized because high concentrations must be used to generate a statistically sufficient number of cancers in a small group of animals with a normal life span of 2 years. However, human exposures to drinking water contaminants include ingestion, inhalation, and dermal exposures that frequently include more than one contaminant and may involve susceptible subpopulations such as fetuses and neonates. The carcinogenic activity of TCE and PCE may be compounded by joint exposure because TCE and PCE appear to share toxic metabolic pathways (44,45).

This study provides information pertinent to current efforts to reduce water contamination. The results of this study, if corroborated by follow-up work, would support the policy of setting standards at levels that reflect protective public health assumptions.

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