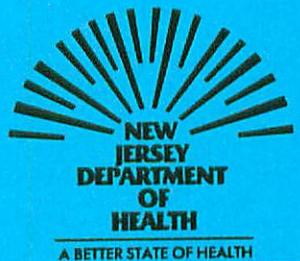
Drinking Water Contamination And The Incidence Of Leukemias And Non-Hodgkin's Lymphomas



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REPORT TO:

THE NEW JERSEY DEPARTMENT OF ENVIRONMENTAL PROTECTION AND ENERGY
AND THE DRINKING WATER QUALITY INSTITUTE

DRINKING WATER CONTAMINATION AND THE INCIDENCE OF LEUKEMIA AND NON-HODGKIN'S LYMPHOMA

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PRODUCED UNDER AN INTERAGENCY AGREEMENT BETWEEN
THE DEPE/BUREAU OF SAFE DRINKING WATER AND THE DEPARTMENT OF HEALTH

May, 1993

TABLE OF CONTENTS

LISTS OF TABLES AND APPENDICES

DRINKING WATER CONTAMINATION AND THE INCIDENCE OF LEUKEMIA AND NON-HODGKIN'S LYMPHOMA

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EXECUTIVE SUMMARY

Since the mid-1970s, several epidemiologic studies have suggested an association between organic drinking water contaminants and increased cancer incidence. The focus to date has been on chlorinated volatile organic compounds (VOCs). In Woburn, Massachusetts, exposure to the solvents, trichloroethylene (TCE) and perchloroethylene (PCE), was linked to a leukemia cluster among children (Lagakos et al., 1986). Bladder cancer was related to surface water chlorination by-products, such as the trihalomethanes (THMs), in both a five state/five metropolitan region case-control study (Cantor et al., 1987) and a case-control study in Massachusetts (Zierler, 1988).

In 1984 New Jersey enacted legislation requiring that all public community water systems monitor semiannually for 14 VOCs, including many chlorinated solvents. In the first year of mandatory testing, approximately 110 water supplies out of 620 supplies in the state had detectable levels of

non-THM VOCs (NJDEP, 1986; Krietzman et al., 1987). These 110 water supplies were primarily those with groundwater sources. The most commonly occurring contaminants were TCE, PCE and 1,1,1-trichloroethane. Many of the sources include improper disposal by commercial and individual users, as well as groundwater pollution at hazardous waste sites.

The New Jersey Department of Health (NJDOH) previously conducted an exploratory study of leukemia incidence in a part of the state with a broad range of contamination. Comparison of data from the New Jersey State Cancer Registry (NJSCR) with the water testing results from 1984-1985 demonstrated a statistically significant association between the concentrations of TCE and PCE and the overall leukemia rate among females from 1979 to 1984 in 27 towns (Fagliano et al., 1987; 1990).

The NJSCR is population-based and reporting is mandatory by law. Information from the NJSCR included age at diagnosis, sex, race, town of residence at diagnosis and histologic type according to the WHO International Classification of Diseases for Oncology (WHO, 1976).

The current investigation expands the earlier NJDOH study from 27 to 75 towns for the 1979-1987 period and also includes non-Hodgkin's lymphomas as well as leukemias. As in the original study, the counties and townships were selected because they were in a portion of the state that 1) was almost completely served by public water supplies and 2) had a wide dispersion of type and concentrations of water contaminants. The area encompasses 1.5 million people.

Poisson regression statistical analysis (summarized in the Table, page v) yielded an age-adjusted rate ratio (RR) for total leukemia among females of 1.43 with a 95% confidence interval (95%CI) of 1.07-1.90 when incidence in

towns in the highest stratum of trichloroethylene (TCE) exposure (>5 parts per billion, ppb, or micrograms/liter) was compared to towns with no detectable TCE in the drinking water. (If the lower bound of the 95%CI is greater than 1.0, then the RR can be considered statistically significant.) For leukemia subcategories, RRs of 2.36 (95%CI 1.03-5.45), 1.57 (95%CI 0.95-2.60), and 1.79 (95%CI 0.90-3.55) were observed in the highest TCE stratum for females with acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML), respectively. (CLL was elevated to the same degree in males.) For females under 20 years old, the RR for ALL was 3.26 (95%CI 1.29-8.28).

Non-Hodgkin's lymphomas (NHL) among women were associated with the highest TCE stratum, with an RR of 1.36 (95%CI 1.08-1.70). In particular, diffuse large cell and high grade NHL (excluding Burkitt's lymphomas) were associated, with RRs of 1.66 (95%CI 1.07-2.59) and 3.17 (95%CI 1.23-8.18), respectively. Perchloroethylene was also associated with incidence of high grade lymphomas among females, but because of the collinearity of TCE and PCE contamination, it was difficult to assess the relative influences of each.

Among males diffuse large cell NHL was also associated with the highest TCE category, RR = 1.59 (95%CI 1.04-2.43), while the RR for non-Burkitt's high grade NHL was non-significantly elevated, 1.92 (95%CI 0.54-6.81).

To study whether there were associations with any history of drinking water contamination utilizing other evidence besides the mandatory monitoring in 1984-1985, the non-systematic drinking water survey data from 1978-1983 was combined with the 1984-1985 mandatory monitoring data study. This combined data showed associations between towns "ever" contaminated with both TCE and PCE and the incidence of childhood ALL and non-Burkitt's high grade NHL among females.

The results of this study suggest a link between TCE and PCE in drinking water and the incidence of certain types of leukemias and NHL. However, the study utilized an ecologic method of determining exposures, i.e., employing geographically aggregated data. This method is suitable for relatively rapid, exploratory work, but is subject to potential misclassification of exposures due to the lack of individual information on degree of exposure to drinking water contaminants and long-term residence. (Nevertheless, in this study the exposure variable comes close to estimating the exposure of all of the population in each exposure group.) Information about potentially confounding exposures was also not available. However, there is no a priori reason to believe that radiation, smoking, occupational exposures, genetic predisposition or infectious agents were differentially distributed among the exposure strata in this study to an extent that would affect these findings. Smoking may not be a sufficiently strong risk factor to be able to cause major bias. Studies with individually-based information on exposures are the next step for investigating the possibility of causality.

Nevertheless, this study is consistent with the efforts by the State and the water utilities that have dramatically reduced contamination in New Jersey (Bono et al., 1992). Because 5 ppb is the maximum contaminant level (MCL) allowed by the U.S. Environmental Protection Agency (U.S.E.P.A) for both PCE and TCE, the observed association of these cancers with contaminants above this level supports maintaining the stringent New Jersey MCLs of 1 ppb.

EXECUTIVE SUMMARY TABLE: STATISTICALLY SIGNIFICANT POSITIVE ASSOCIATIONS

Exposure	Sex	Outcome	RR
TCE >5ppb	Females	Total leukemia	1.4
	''	ALL	2.4
	''	Childhood ALL (0-19 years)	3.3
	''	Total NHL	1.4
	''	Diffuse large cell NHL	1.7
	''	Non-Burkitt's high grade NHL	3.2
	Males	Diffuse large cell NHL	1.6
PCE >5ppb	Females	Non-Burkitt's high grade NHL	2.7

INTRODUCTION

In 1984, New Jersey enacted the landmark amendments (also known as A-280) to the New Jersey Safe Drinking Water legislation, requiring all public community water systems to monitor semiannually for 14 volatile organic compounds (VOCs), including many chlorinated solvents, and for two non-VOCs. Since 1981 water supplies serving more than 10,000 have also been tested for trihalomethanes (THMs), which are by-products of the chlorination process.

In 1984-1985, during the first rounds of mandatory testing, roughly 110 water supplies out of 620 supplies in the state, serving about 20 percent of the state's population, had detectable levels of non-THM VOCs (NJDEP, 1986; Krietzman et al., 1987). The most commonly occurring non-THM VOCs were trichloroethylene (TCE), tetrachloroethylene (or perchloroethylene, PCE), and 1,1,1-trichloroethane. Sources may include improper disposal by commercial and individual users, as well as groundwater pollution from hazardous waste sites. As a result of the monitoring and subsequent regulatory actions, New Jersey drinking water has been greatly improved (Bono et al., 1992).

Under the Safe Drinking Water Act, New Jersey also established maximum contaminant levels (MCLs) in 1989 for the 14 VOCs in community water systems. These MCLs have been mostly based on laboratory animal toxicology with some corroboration from occupational epidemiology.

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 ALL, among children (Lagakos et al., 1986), while another recent study in Massachusetts observed an association between leukemia and PCE (Aschengrau et

al., 1992). Bladder cancer was related to surface water chlorination by-products, such as the trihalomethanes (THMs), in a five state/five metropolitan region case-control study (Cantor et al., 1987), in case-control studies in Massachusetts (Zierler, 1988) and Colorado (McGeehin et al., 1992), and in a recent statistical meta-analysis of all epidemiologic studies on bladder cancer and THMs (Morris et al., 1992).

The New Jersey Department of Health (NJDOH) 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 (NJSCR) and from the water testing program demonstrated a statistically significant association of the concentrations of TCE and PCE with the overall leukemia rate (from 1979 to 1984) among females residing in a 27 town study area (Fagliano et al., 1987; 1990). The current investigation expands the geographic scope of that earlier study to 75 towns, examines disease incidence for a longer time period (1979-1987), and includes non-Hodgkin's lymphomas (NHL) as well as leukemias. However, as with the earlier study, there were no interviews to obtain further information about overall exposures that might be related to these diseases. The hypotheses were: 1) that the incidence of leukemia in is associated with exposure to TCE and/or PCE; 2) that childhood leukemia, in particular, is associated with TCE and/or PCE; and 3) that NHL is associated with TCE and/or PCE. 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 (Linet, 1985; Magrath, 1990).

METHODS

Study Population

The study area encompassed 75 municipalities with a 1980 population of almost 1.5 million (Table A1, Appendix A) 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 counties and municipalities were selected because they were in a portion of the state that 1) was 95% served by monitored public water supplies and 2) was primarily urban and residential so that town coding in the NJSCR is likely to be accurate (i.e., rural route numbers and postal boxes are not complicating factors). Municipalities were included only if more than 80% of the population was served by a water utility (three towns were under 90%). Only in four towns were more than 10% of the population served by two different supplies.

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 infrequent health outcomes, such as leukemias and non-Hodgkin's lymphomas.

Generally, the study area was a region of relative out-migration between the 1970 and 1980 Censuses, with an average loss of about 5 percent. In each of the exposure strata (described below) less than 10 percent of the municipal population had in-migration greater than 10 percent between 1970 and 1980. This pattern is consistent with the interpretation that cases would have tended not be new immigrants to the study area, but that there would have tended to be a small loss of cases from the study area.

Disease Measurement

Incident cases of primary leukemias and non-Hodgkin's lymphomas (NHL) from 1979-1987 were obtained from the NJSCR. The NJSCR is population-based and reporting is mandatory by law. However, case ascertainment was augmented by death certificates (see below). The overall ascertainment 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 WHO International Classification of Diseases for Oncology (WHO, 1976) or ICD-O.

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 (Non-Hodgkin's Lymphoma Pathologic Classification Project, 1982) and the ICD-O Field Trial Edition (WHO, 1988). 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 (Burke, 1990). High grade NHL was also examined without Burkitt's lymphoma because of the possible viral etiology of the latter (Haluska et al., 1990). In addition, mucocutaneous lymphomas were grouped separately but included with NHL. The corresponding ICD-O histology codes are shown in Table 1. (A short review of basic facts about leukemias and NHL is given in Appendix B).

Death certificates accounted for 15% of the leukemia and 8% of the NHL ascertainments. 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.

Exposure Assessment

The exposure data were derived from (1) the 1984-1985 measurements of four THMs and fourteen other VOCs in the mandatory monitoring program administered by New Jersey Department of Environmental Protection and Energy (NJDEPE) for public water supplies (Krietzman et al., 1987) and (2) from historical monitoring data conducted in 1978-1983 by NJDEPE and NJDOH. The 1984-1985 data were corroborated by the water purveyors. The NJDEPE and the purveyors also provided details on the distribution system size, well or surface water use, and patterns of water purchases among systems. Any significant changes in water supply and use between 1970 and 1985 were noted by the purveyors or NJDEPE. Such changes consisted largely of closings of contaminated wells during the 1980-1984 period. 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 utilized an average derived from a previously generated month-to-month analysis conducted as part of a NJDOH/Centers for Disease Control study (Bove et al., 1992). This procedure differed from the earlier leukemia study (Fagliano et al., 1990).

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 (Bove et al., 1992). The average and maximum concentrations of THMs, total non-THM VOCs, TCE and PCE were estimated from the 1984-1985 data 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 despite the fact that some wells in many groundwater systems probably supplied specific areas. It was not possible to ascertain whether sampling sites were selected to maximize the likelihood of detecting contaminants, in contrast to locations representative of the system. 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 from another system, the summary results were modified by amounts proportional to the estimated dilution factor, assuming complete mixing. In some cases bulk purchases depended upon the season. Furthermore, it is possible that short-term high levels were undetected because of the monitoring schedule. Ultimately, a single summary average and maximum concentration for each contaminant was assigned to an entire municipality.

In view of the potential errors in determining the exposures, exposure variables were categorized. Based on the 1984-1985 VOC concentrations, towns were grouped into categories of total non-THM VOCs (TVOC), TCE, PCE or THM summary concentrations after empirical inspection of the distribution of values.

Four categories represented TVOC summary exposures for the 1984-1985 period: <0.1 (unexposed), 0.1-5, >5-20 and >20 parts per billion (or ppb, equivalent to microgram per liter). The lowest exposure range represents

municipalities for which there were no detectable VOCs. 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. Environmental Protection Agency (USEPA) maximum contaminant levels for TCE and PCE were set at 5 ppb (USEPA, 1985, 1989a) and because it included a population of sufficient size to provide useful statistical power for the analyses. Other categories were also examined but the results were not notably different. 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 TVOC level was 92.9 ppb and the highest assigned THM level was 87.6 ppb. Due to the low concentrations and small populations involved with the other non-THM VOCs, the power to detect increased incidence was limited. Therefore, analysis was limited to presence or non-detection of these other contaminants. Heavy metal contamination was not a problem in this area.

For further description of the distribution of TCE and PCE contamination among the study towns see Appendix C.

NJDEPE and NJDOH surveys of VOCs during the 1978-1983 period were used to provide corroborating evidence for the use of the 1984-1985 data 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 not systematic and because the 1984-1985 data were confirmed by the water purveyors. Because the 1978-1983 data were usually collected in response to known contamination, categorizing a system as significantly contaminated is more clearly defined than categorizing a system as uncontaminated. Sampling and laboratory quality assurance and quality control during the mandatory monitoring period than in the late 1970s. Further, one water system did not

have historical data and three had only one historical measurement, a few of which were raw water (prior to treatment) samples. Thirteen water systems were only represented by raw water samples. In addition, the historical results for a quarter of the municipalities are based on sampling of ten bulk purchase water suppliers, nine of which had distribution system samples. Recognizing that historical data are of variable quality, towns were grouped into categories: low/none, medium and high average summary levels for TCE, PCE and TVOC contamination. However, for consistency, this division corresponds approximately to <0.1, 0.1-5.0, and >5.0 for TCE and PCE and <0.1, 0.1-20.0, and >20.0 for TVOCs. If there was evidence that remediation or closure of contaminated wells resulted in reduced concentrations in later years, the contaminant levels in earlier years were used for the average summary level. The probable maximum summary levels of contamination were higher than for the 1984-1985 period, with the highest assigned municipal levels for PCE and TCE around 100 ppb. The 1978-1983 data are further described in Appendix D.

Data Analysis

Leukemia and lymphoma incidence data were calculated for each exposure category. For illustration, the populations by age and sex in each TVOC, TCE, and PCE category are summarized in Table A2, located in Appendix A.

Log-linear regression with a Poisson distribution model (Breslow et al., 1983) was used to generate incidence rate ratios (RR) and the 95% confidence intervals (CI) within the study area. Poisson regression analysis provides a practical method for modeling the occurrence of rare events, such as the incidence rates of leukemia and NHL (Kleinbaum et al., 1988). Poisson regression fitted the age- and sex-specific count of cases in towns grouped by the broad exposure strata, offset by the logarithm of the stratum-specific population. Analysis was performed by EGRET software (SERC, 1990), which

provides coefficients of effect relative to the lowest level of a variable (e.g., the group of towns with the lowest contamination level). Rate ratios and their confidence intervals (CI) relative to the lowest stratum were computed by the software. The use of categorical approximation in Poisson regression methods used for analysis (see below) does not require a priori the assumption of an exponential relationship between exposure and disease incidence.

The modeling strategy attempted to determine exposure rate ratios, adjusted for age, and included added terms to look at other 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. (There were only minor differences in RR estimation with stratification into 12 age subgroups.) Since Fagliano et al. (1990) reported an association between incidence of leukemia among females and drinking water contaminants, cases were grouped by sex for separate analysis.

The co-influence of exposure variables, including TCE and PCE, was also examined by cross-tabulation of cases in each combination of exposure categories. The results of the cross-tabulation were analyzed by Poisson regression.

Municipal average annual household income (from the 1980 Census) and estimated carcinogenic air emissions tabulated on the municipality level from the 1987 Toxics Release Inventory (USEPA, 1989b) were also analyzed for potential confounding or effect modification on the estimates for drinking water contaminants exhibiting significant association with leukemias or NHL. The average annual household income variable represented the division of towns into four groups: <$20,000, $20,000-24,999, $25,000-29,999 and ≥$30,000. For

carcinogenic emissions to air, a variable (TRI) was created to combine municipalities into four categories with similar population size. Compounds on this list included known, probable and possible carcinogens, using USEPA (1986) terminology. The resulting categories of fugitive plus stack air emissions of carcinogens from commercial and industrial sources were: under 300 lb/yr, 300-2,999 lb/yr, 3,000-29,999 lb/yr, and ≥30,000 lb/yr. The highest carcinogenic fugitive, stack, and total emissions for a municipality were 180,000 lb/yr, 250,000 lb/yr, and 304,000 lb/yr, respectively. It should be noted that the TRI data are based entirely on estimates reported by industry, does not include precise geographical information, and would require dispersion modeling to approximate actual air concentrations on a municipality basis.

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 (Table 2). (These cases excluded those ascertained by death certificate data only.) Age and sex distributions are listed for acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML). As expected, cases of ALL were predominantly in the 0-19 age bracket at diagnosis. All other categories of leukemia were primarily in the 50+ age groups and their incidence rate increased with age. 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), not including those ascertained by death certificate data only; 841 cases of among males and 817 among females of all races (Table 2). About 25% were not classified by specific histology. The incidence rate increased with age and most cases were in the 50+ age groups. The majority of cases were low and intermediate grade lymphomas. The age specific incidence rates (including death certificate ascertainments) were within 10% of the State rates.

Because leukemia and NHL incidence rates were similar between whites and non-whites in the study area, and because of the small number of cases among non-whites in municipalities with higher levels of contamination, all races were combined in the analyses presented here.

Inclusion of NJSCR cases ascertained only by death certificates did not affect the results, except as noted.

Association of Incidence with Total Non-THM Volatile Organic Compounds (TVOCs)

A significant association between leukemia incidence among females and residence in towns in the highest exposure stratum (>20 ppb) of non-THM TVOCs from the 1984-1985 monitoring period was observed (Table 3). The age-adjusted rate ratio (RR) of leukemia incidence among females, comparing the highest non-THM TVOC exposure category to the lowest (unexposed) exposure stratum, was 1.42 with a 95% confidence interval (95%CI) of 1.05-1.90. Similarly, the RR for NHL among women in the highest exposure stratum was 1.24 (95%CI 0.97-1.57). Among males there was a less significant association, RR = 1.20 (95%CI 1.00-1.44), between one intermediate level (5.1-20.0 ppb) of TVOCs and NHL incidence.

Association of Incidence with Trichloroethylene (TCE)

For leukemias among females the RR of the highest TCE exposure stratum (>5 ppb) to the unexposed (none detected) stratum (Table 4) was 1.43 (95%CI 1.07-1.90) for total leukemias and 2.36 (95%CI 1.03-5.45) for ALL. The RRs for CLL and CML were elevated, 1.57 (95%CI 0.95-2.60) and 1.79 (95%CI 0.90-3.55), respectively. Among males there was no association of total leukemias with TCE, but the RR for CLL was elevated, 1.49 (95%CI 0.97-2.30).

The incidence rates of NHL among females (Table 5) 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 1.36 (95%CI 1.08-1.70). Certain groups of NHL histologies exhibited elevated RRs among females in the highest TCE category: 2.43 (95%CI

0.97-6.05) for high grade NHL and 1.46 (95%CI 1.03-2.05) for intermediate grade NHL. Statistically significant elevations of RRs in individual subgroups include 1.66 (95%CI 1.07-2.59) for the intermediate grade NHL grouping, diffuse large cell/reticulosarcoma, and 3.17 (95%CI 1.23-8.18) for the high grade NHL, excluding Burkitt's lymphomas. None of the Burkitt's lymphomas among females were from municipalities in the highest TCE category.

Males also exhibited a significantly elevated rate of the diffuse large cell/reticulosarcoma NHL, 1.59 (95%CI 1.04-2.43), and a non-significantly elevated rate for the non-Burkitt's group of high grade NHL, 1.92 (95%CI 0.54-6.81), respectively, in the highest TCE category.

(The age/sex distribution of cases by TCE category is shown in Tables A3 and A4 of Appendix A.)

The Effect of Including 1978-1983 TCE Data

In general, there was not much difference among males or females in the observed RRs with the inclusion of data from 1978-1983, such that the TCE variable represented all data from 1978-1985. However, there was reduced strength of association of the highest TCE category with CLL among females, RR = 1.32 (95%CI 0.79-2.21), and with diffuse large cell NHL among females, RR = 1.29 (95%CI 0.84-1.99). In contrast, the association of non-Burkitt's high grade NHL among females with the highest TCE exposure category was strengthened, RR = 5.79 (95%CI 1.74-19.2).

Childhood Leukemia: Association with TCE

Childhood leukemia among females, particularly ALL, was significantly elevated in the highest category of TCE exposure when compared to the unexposed stratum. The RR was 3.26 (95%CI 1.29-8.28) for females diagnosed

with ALL before their 20th birthday, based on six cases in the highest TCE exposure category. For females diagnosed before their 5th birthday, the RR was 4.54 (95%CI 1.47-10.6), based on five cases. For all female childhood leukemias, the RR was 2.23 (95%CI 0.98-5.10), while for female childhood NHL the RR was 1.68 (95%CI 0.37-7.59). Among young males there were no significant associations.

Inclusion of cases ascertained only by death certificates affected the results because an additional six cases resided in municipalities with no detectable TCE during the 1984-1985 period. 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) in the highest TCE stratum. When analyzed by combined 1978-1985 data, the RR for female childhood ALL in the highest category TCE exposure was 3.60 (95%CI 1.31-9.93) since the additional six cases resided in towns with intermediate TCE levels.

Association of Incidence Rates with Perchloroethylene (PCE)

Overall, PCE contamination was not significantly associated with leukemia or NHL incidence. However, among females the rate ratios of high grade NHL, with or without Burkitt's lymphomas, were associated with the highest PCE exposure category, RR = 2.66 (95%CI 1.27-5.60) and 2.74 (95%CI 1.20-6.26), respectively (Tables 6-7). This was the only histologic grouping that was significantly associated with both TCE and PCE. The incidence of childhood ALL among females was non-significantly elevated in the highest PCE category with an RR = 1.78 (95%CI 0.75-4.23). It was difficult to separate the relative influences of TCE and PCE (see Appendix E) because of the degree of

correlation (R=0.63) between 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 (i.e., "ever" contaminated with PCE), PCE was non-significantly associated with non-Burkitt's high grade NHL among females, RR = 2.19 (95%CI 0.66-7.27), and childhood ALL among females, RR = 2.10 (95%CI 0.84-5.26).

Association of Incidence Rates with THMs, Benzene, Other VOCs, Gross Alpha Radiation, and Source of Water

No association was detected between leukemia or NHL incidence and THMs or with other non-THM VOCs, such as benzene, carbon tetrachloride, 1,1,1,-trichloroethane 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.

Although several towns contaminated with high levels of both TCE and PCE were also contaminated with 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. In addition, there was no association between AML and benzene.

Gross alpha radiation levels in water (a measurement which does not include radon) were also available. Average levels were all below 5 picocuries per liter, the current USEPA standard. Gross-alpha radiation (greater or less than 1 picocurie per liter, with about one-third of the population in the higher category) was not associated with the incidence of total leukemia or NHL.

Assessment of Confounding by Other Factors

In general, adjusting for household income and carcinogenic toxic air releases (TRI) on a municipality level did not alter the observed association of leukemias and NHL with TCE, with the exception of increasing the observed RR with TCE for non-Burkitt's high grade NHL among females (see Appendix F).

The TRI database was inspected for the presence of specific carcinogens among the air emissions. Of benzene, TCE and PCE, only the latter two were reported to be released in study area municipalities. Of all the lymphohematopoietic cancers examined, only the incidence rates of AML among males over age 70 were significantly associated with the releases of TCE. None were linked to PCE.

DISCUSSION

Under the New Jersey Safe Drinking Water Act, MCLs have been established for the most prevalent of the VOCs contaminating the drinking water supply. The MCLs are based on laboratory animal toxicology, with the exception of benzene. However, there is considerable uncertainty in extrapolating that data to potential effects from human exposure to low levels of environmental contamination over many years. Furthermore, the effects of occupational exposures, when such studies are available, may not be representative of what happens in the population as a whole due to the presence of individuals in certain age/sex/race groups who may be more sensitive to particular chemicals and/or are underrepresented in the particular occupational group.

Because some of the regulated VOCs are considered to be probable human carcinogens and because of an earlier study in Woburn, Massachusetts, linking exposure to public supply well water, contaminated with as much as 267 ppb of TCE and 21 ppb of PCE, to increased incidence of leukemia (Lagakos et al., 1986), the NJDOH decided that it would be worthwhile to compare the results of mandatory monitoring of public drinking water in New Jersey with data from the NJSCR. An initial investigation conducted by Fagliano et al. (1987, 1990) observed an association between both TCE and PCE and the incidence of leukemia among females in a 27 town study area. For the current investigation the original study area was expanded to include a larger exposed and unexposed population in order to enhance the power to detect associations for specific histological groupings of leukemia and NHL.

The study of 75 municipalities in four northern New Jersey counties reported here found a statistically significant association between VOC contamination in drinking water and the incidence of leukemia and NHL during the 1979-1987 period. The study had statistical power to detect rate ratios

of 1.5-3.0 for specific histologic groupings of leukemia and NHL, given the overall incidence rates of those groupings.

Improvements in the current study over the previous NJDOH study included 1) increased sample size; 2) an improved exposure database because the public water supply monitoring data from 1984-1985 were given an extensive quality control review in conjunction with other NJDOH studies; and 3) an improved calculation of exposures from the 1984-1985 data based on lessons learned and methods developed for other NJDOH projects. The exposure calculations benefited, in particular from the availability of treatment plant samples, in addition to distribution system samples and from monthly summary exposure estimates derived with greater attention to seasonal variation.

In addition, this study also used non-systematic drinking water survey data from 1978-1983. While the quality of that data is less than that from the mandatory monitoring (see Methods), the 1978-1983 data are useful for identifying and/or corroborating the presence of specific contaminants at points in time relative to the dates of diagnosis that are more relevant to the latency period (5-20 years) that is believed to characterize adult leukemo- and lymphomagenesis by radiation and occupational exposure to chemicals (Linet, 1985; Magrath, 1990). If childhood leukemia and NHL have shorter latency periods, the available exposure may be more germane.

Significantly elevated rate ratios of one or more of the outcomes studied were observed in association with the presence of more than 5 ppb of TCE and more than 5 ppb of PCE in drinking water. These results extend the findings of the previous NJDOH study and are also consistent with the study in Woburn, Massachusetts.

Trichloroethylene

Rate ratios comparing the highest stratum of TCE exposure (greater than 5 ppb) with the unexposed (none detected) stratum demonstrated statistically significant associations, particularly with childhood ALL among females and non-Burkitt's high grade NHL among females, for which RRs were greater than 3.0. Rate ratios of similar strength were observed after analysis of both the 1984-1985 mandatory monitoring data or the combined 1978-1985 data. The associations were attributable in large part to elevated incidence rates in the substratum composed of the jointly highest TCE and PCE categories in either data set. Notably, non-Burkitt's high grade NHL and diffuse large cell NHL, which are also aggressive lymphomas (Burke, 1990), tended to be positively associated with TCE among both males and females.

Perchloroethylene

The highest stratum of PCE contamination in the 1984-1985 data was also associated with non-Burkitt's high grade NHL among females, while analysis of the combined 1978-1985 data also revealed an association with female childhood ALL. Because of collinearity of TCE and PCE contamination, it was difficult to assess the relative influences of each.

Benzene

The known human leukemogen, benzene, was found in the water supplies of three of the four towns in the highest combined 1984-1985 TCE and PCE exposure categories and four of the six towns in the highest combined 1978-1985 TCE and PCE exposure categories. (However, the data on benzene during the earlier period were less complete and consistent than for PCE and TCE.)

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

alone whether with the 1984-1985 data or with the combined 1978-1985 database. In addition, AML, the type of leukemia most often associated with benzene in human studies (Austin et al., 1987; Rinsky et al., 1987) was not associated with benzene contamination of drinking water in this study. However, it has been suggested by some that benzene exposure may also be associated with other forms of leukemia and with NHL (Wong, 1987).

Mixtures of Contaminants

As noted above, it was difficult to distinguish the influence of individual compounds from the association of the mixture with leukemias and lymphomas. Thus, the significant exposure of the study can be viewed as a mixture of certain VOCs. The effect of mixtures of contaminants has been of major interest in environmental health. For example, the studies in Woburn, Massachusetts, involved mixtures of TCE and PCE. However, it should be noted that there may be additional organic substances not detected by the testing methods. There were no heavy metal contamination problems in the study area.

Little is known about the degree of carcinogenic interaction between probable carcinogenic compounds, although some theories have been proposed. Carcinogenic compounds or their metabolites that affect the same organ, cell, enzyme, or portion of DNA might have a synergistic effect. A compound might also have an indirect effect on a specific carcinogenic mechanism of another compound or might produce (or "promote") changes at a later stage in a carcinogenic mechanism initiated by another.

Toxic Release Inventory Carcinogens

Because the Toxic Release Inventory (TRI) from 1987 (USEPA, 1989b) was available on a municipality level, it was used as an exploratory tool, serving as a surrogate for occupational and environmental exposures to toxic

substances in air. However, TRI is probably temporally inappropriate, TRI is based entirely on estimates reported by the regulated companies, and in the absence of dispersion modeling, TRI data may not reflect air concentrations by municipality. Specific ambient outdoor air data were not available on a municipality level.

Estimated air releases of total or specific known, probable, and possible human carcinogens were, with one exception, not associated with the incidence rate of NHL or leukemia in either sex. While non-Burkitt's high grade NHL among females was significantly associated, the observed association with TCE in water was increased when the TRI data was included in the model.

Potential Causes and Confounders

Well known etiologic factors in leukemia and lymphoma include certain genetic traits, ionizing radiation, infectious agents, DNA-repair enzyme deficiencies, and certain chemicals (Linet, 1985; McKinney et al., 1987, 1990; Committee on the Biologic Effects of Ionizing Radiation, 1990; Magrath, 1990). In particular, occupational exposures to benzene have been linked to leukemias, especially AML, and lymphomas (Austin et al., 1987; Rinsky et al., 1987; Wong, 1987). Chlorophenoxy herbicides have been linked by some to the incidence of NHL (Hardell et al., 1981; Hoar et al., 1986), but not by others (Johnson, 1990). The relative risk of leukemia, principally the AML form, among smokers is moderately elevated (Sandler and Collman, 1987; Kinlen and Rogot, 1988; Severson et al., 1990; Brownson et al., 1991). Recent evidence also links multiple myeloma with smoking (Mills et al., 1990). There is no *a priori* reason to believe that radiation, smoking, occupational exposures, genetic predisposition or infectious agents are differentially distributed among the exposure strata in this study to an extent that would affect these findings.

Occupational studies of TCE and PCE exposures have found inconsistently elevated rates for leukemias and lymphomas, as well as for malignancies of the kidney, cervix uteri and other sites (Blair et al., 1979; Olsson and Brandt, 1980; Katz and Jowett, 1981; Axelson, 1986; Brown and Kaplan, 1987). However, most studies were small and had short follow-up times. Inhaled PCE significantly increased the percentage of young F344/N rats that develop a mononuclear cell leukemia which arises spontaneously in senescent rats of this strain (NTP, 1986). Laboratory studies in mice have demonstrated elevated hepatic carcinomas after exposure to TCE (NTP, 1986) or PCE (NTP, 1986). Based on these rodent studies, both TCE and PCE have been classified as probable human carcinogens by USEPA (1985, 1989a), meaning that there is sufficient evidence from animal studies, but inadequate evidence from epidemiologic studies. Human cancer risk could involve different organs or cell types from those in the rodent studies.

That the observed associations of drinking water contaminants with adult leukemia and NHL were stronger among females may be partly due to less smoking and occupational carcinogen exposure among women, compared to men. The increased background rates among males might make it more difficult to detect rates elevated after exposure to contaminated drinking water.

The potential relationship between parental occupation and the incidence of childhood cancer (Savitz and Chen, 1990) is another area in which confounding exposures might have an effect on associations observed in this study. However, the studies of this effect are inconsistent and much remains to be clarified.

Limitations

This study utilized the ecologic method of determining exposures, useful for inexpensive exploratory investigation in which geographically aggregated

data are analyzed. This method is subject to potential misclassification of exposure due to the lack of individual information. Some sources of exposure misclassification may be change of residence by subjects, variability in use of tap water, and existence of some private wells in the study area. In this study, since the exposure variable comes close to estimating the exposure of all of the population in a group, there is no ecologic bias (Greenland and Morgenstern, 1989).

Major simplifying exposure assumptions in this study are: 1) that there was complete mixing of contaminants throughout the water system in a municipality, even though wells in some groundwater systems tend to supply nearby areas; 2) that within an age-sex group there are similar water use patterns in all exposure strata; 3) that the observed concentrations of contaminants are representative of contamination back to the early 1970s (i.e., the relevant exposure period, considering adult disease latency); and 4) that each case lived in the municipality listed in the Cancer Registry (or one with similar exposure) during the relevant exposure period prior to diagnosis. There was no information on home water filtration, but its prevalence was low until recent years. Notably, this type of exposure misclassification in "ecologic studies in which exposure of groups is characterized by a single common measure" (vs "proportion of individual exposed") tends to reduce the observed effect (Brenner et al., 1992, p.92).

The actual exposure of individuals to water contaminants varies according to the quantity of water consumed from the tap and to the amount of inhaled volatilized compounds during non-drinking uses, such as showering, laundering and dish washing. Individual exposure from these routes may amount to 100-500% of that from ingestion alone (Shehata, 1985; Andelman, 1985; McKone, 1987; Jo et al., 1990). In addition, dermal absorption also occurs and may

represent as much as 50-100% additional exposure. This assessment can be complex. However, there is no reason to believe that uses of water other than for drinking differ across exposure strata.

In towns with the highest drinking water exposures to TCE and PCE, drinking water was probably the most important non-occupational source of exposure to these two solvents on a daily basis, especially when considering total body exposure to water contaminants due to both ingestion and indoor air inhalation routes. In comparison with outdoor air exposure to these compounds, using measurements from the early 1980's in several urban Northern New Jersey towns near the study area (Wallace et al., 1985; Hartwell et al., 1987; Harkov et al., 1988), water contaminated with TCE or PCE over 10-25 ppb would have represented the more significant exposure.

The desirability of individual lifetime carcinogenic exposure information (e.g., smoking and occupation) is clear. However, as stated above, there is no a priori reason to believe that radiation, smoking, occupational exposures, genetic predisposition or infectious agents are differentially distributed among the exposure strata in this study to an extent that would affect these findings. In addition, smoking does not appear to be a sufficiently strong risk factor to be able to cause major bias.

Therefore, observations should be interpreted cautiously because: 1) exposure misclassification could lead to underestimation of effects of exposure, 2) unmeasured confounding by other potential causes of leukemias and NHL could introduce bias leading to under- or overestimation of effects of exposure, 3) unmeasured effect modification could lead to under- or overestimation, and 4) an observed association could be due to chance. Studies with an individually based design, such as case-control studies, are the next step for elucidating a causal connection.

Conclusions

The results suggest a link between TCE and PCE at levels greater than 5 ppb in drinking water and the incidence of certain types of leukemias and non-Hodgkin's lymphomas. They are consistent with the results of the prior NJDOH investigation. Further study would be useful to pursue whether such low level exposures could contribute to elevated leukemia and NHL incidence.

This study provides useful information for current efforts to reduce water contamination in New Jersey. Current water quality in New Jersey reflects the stringent standards that were adopted in the State in 1989 (Bono et al., 1992). The results of this study, if corroborated by follow-up work, would support the policy of setting standards that reflect protective public health assumptions.

ACKNOWLEDGMENTS

The authors wish to acknowledge the Bureau of Safe Drinking Water (BSDW) in the Department of Environmental Protection and Energy, as well as the New Jersey State Cancer Registry (NJSCR) of the Department of Health, without whose information and assistance this research could not have happened. In particular, we thank Barker Hamill, Bill Dietze, Brian Keune, Paul Schorr, Sandy Krietzman and all the other helpful people of BSDW, as well as Toshi Abe and Annemarie Anepete of the NJSCR.

We thank Maureen Hatch, PhD, of Columbia University, Charles Lynch, MD PhD, of the University of Iowa, Dale Sandler, PhD, of the National Institute of Environmental Health Sciences, and Daniel Wartenberg, PhD, of the University of Medicine and Dentistry of New Jersey, for their critiques.

We also thank Rebecca Parkin, former Assistant Commissioner of the Division of Occupational and Environmental Health, and Janet Schoenberg, Program Manager in the Division of Epidemiology and Communicable Disease Control for their helpful discussions and their skillful editing.

Other reviewers to thank are Diana Kiel, former Assistant Director of the Environmental Health Service (EHS), Michael Berry of the EHS, and Nancy Hall, formerly of the Occupational Health Service.

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TABLES

Table 1. LEUKEMIA AND NON-HODGKIN'S LYMPHOMA CLASSIFICATIONS BY ICD-O CODE (WHO, 1976; WHO, 1988)

CLASSIFICATION	ICD-O CODE
TOTAL LEUKEMIAS	9800-9940
ACUTE LYMPHOCYTIC LEUKEMIA (ALL)	9821
CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)	9823
ACUTE MYELOGENOUS LEUKEMIA (AML)	9861, 9866, 9890-91
CHRONIC MYELOGENOUS LEUKEMIA (CML)	9863-9864
OTHER	9822, 9824-50, 9862, 9865, 9870, 9880, 9910, 9930, 9940
UNSPECIFIED	9800-10, 9820, 9860
TOTAL NON-HODGKIN'S LYMPHOMAS (NHL)	WORKING FORMULATION GROUPS A-J: 9590-93, 9600-42, 9670-9701, 9750
LOW GRADE NHL	
A. DIFFUSE SMALL CELL, NON-CLEAVED	9611, 9620, 9670-71
B. FOLLICULAR SMALL CELL	9693-96
C. FOLLICULAR MIXED SMALL/LARGE CELL	9691-92
INTERMEDIATE GRADE NHL	
D. FOLLICULAR LARGE CELL	9642, 9697-98
E. DIFFUSE SMALL CELL, CLEAVED	9621-22, 9630-31, 9672-74
F. DIFFUSE MIXED SMALL/LARGE CELL	9613-14, 9616, 9675-76
G. DIFFUSE LARGE CELL/RETICULOSARCOMA	9623-24, 9632-34, 9640, 9680-83
HIGH GRADE NHL	
H. IMMUNOBLASTIC	9612, 9641, 9684, 9703
I. LYMPHOBLASTIC	9602, 9685
J. UNDIFFERENTIATED NON-BURKITT'S	9600, 9686
J. UNDIFFERENTIATED BURKITT'S	9687, 9750
MUCOCUTANEOUS NHL	9700-02
OTHER NHL, NOT SPECIFIED OR NOT CLASSIFIABLE INTO GRADES	9590-93, 9601, 9610, 9615, 9690

Table 2. Number of Cases and Average Annual Incidence Rates for Leukemia and non-Hodgkin's Lymphoma (per 100,000 Population) in the Northern New Jersey Study Area by Age Category and Sex, 1979-1987; NJDOH, 1993.

a. TYPES OF LEUKEMIA

MALES

AGE	ALL	CLL	AML	CML	OTHER	UNSPECIFIED	TOTAL NUMBER	AVERAGE ANNUAL INCIDENCE/100,000
0-19	33	1	9	2	1	14	60	3.1
20-49	15	11	24	19	6	21	96	3.7
50-69	12	105	63	35	22	34	271	21.0
70+	4	88	59	20	15	50	236	57.1
	64	205	155	76	44	119	663	

FEMALES

AGE	ALL	CLL	AML	CML	OTHER	UNSPECIFIED	TOTAL NUMBER	AVERAGE LEUKEMIA INCIDENCE/100,000
0-19	36	1	7	1	0	8	53	2.8
20-49	3	4	19	20	2	20	68	2.4
50-69	5	48	40	25	11	28	157	10.5
70+	10	96	55	24	4	60	249	35.4
	54	149	121	70	17	116	527	

b. TYPES OF NON-HODGKIN'S LYMPHOMAS

MALES

AGE	LOW GRADE	INTERMEDIATE GRADE	HIGH GRADE	MUCO-CUTANEOUS	NON-SPECIFIC	TOTAL NUMBER	AVERAGE ANNUAL INCIDENCE/100,000
0-19	2	9	4	0	4	19	0.9
20-49	38	77	14	2	28	159	5.8
50-69	116	161	10	3	94	384	29.8
70+	71	124	6	1	77	279	67.6
	227	371	34	6	203	841	

FEMALES

AGE	LOW GRADE	INTERMEDIATE GRADE	HIGH GRADE	MUCO-CUTANEOUS	NON-SPECIFIC	TOTAL NUMBER	AVERAGE ANNUAL INCIDENCE/100,000
0-19	0	2	7	0	8	17	0.9
20-49	33	40	6	1	29	109	3.7
50-69	99	120	11	6	94	330	22.1
70+	75	175	11	4	96	361	51.3
	207	337	35	11	227	817	

Table 3. Number of Reported Cases and Age-Adjusted Rate Ratios (RR) for Leukemias and Non-Hodgkin's Lymphomas (NHL) in the Northern New Jersey Study Area, 1979-87, by Total VOC (TVOC) Exposure Category and Sex, All Races; NJDOH, 1993.

TVOC Exposure (ppb)	Cases		Rate Ratios (RR and 95%CI)	
	Males	Females	Males	Females
a. Total Leukemias				
<0.1	306	220	1.0	1.0
0.1-5.0	190	160	0.90 (0.75-1.08)	1.05 (0.86-1.29)
5.1-20.0	111	92	0.88 (0.71-1.10)	1.03 (0.80-1.31)
>20.0	56	55	0.98 (0.74-1.31)	1.42 (1.05-1.90)
Total	663	527		
b. Total Non-Hodgkin's Lymphomas				
<0.1	357	364	1.0	1.0
0.1-5.0	237	237	0.96 (0.81-1.13)	0.95 (0.80-1.12)
5.1-20.0	177	135	1.20 (1.00-1.44)	0.91 (0.75-1.11)
>20.0	70	81	1.04 (0.81-1.35)	1.24 (0.97-1.57)
Total	841	817		

Table 4. Number of Reported Cases and Age-Adjusted Rate Ratios (RR) for Leukemias in the Northern New Jersey Study Area, 1979-87, by Trichloroethylene (TCE) Exposure Category and Sex, All Races; NJDOH, 1993.

TCE Exposure (ppb)	Cases		Rate Ratios (95%CI)	
	Males	Females	Males	Females
a. 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		
b. Acute Lymphocytic Leukemia (ALL)				
<0.1	45	25	1.0	1.0
0.1-5.0	16	22	0.72 (0.31-1.67)	1.85 (1.03-3.70)
>5.0	3	7	0.75 (0.18-3.18)	2.36 (1.03-5.45)
Total	64	54		
c. Chronic Lymphocytic Leukemia (CLL)				
<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		
d. Acute Myelogenous Leukemia (AML)				
<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		
e. Chronic Myelogenous Leukemia (CML)				
<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		
f. Other Specified Leukemias				
<0.1	29	10	1.0	1.0
0.1-5.0	11	6	0.88 (0.51-1.51)	1.02 (0.53-1.97)
>5.0	4	1	0.81 (0.32-2.04)	1.39 (0.54-3.58)
Total	44	17		
g. Unspecified Leukemias				
<0.1	81	71	1.0	1.0
0.1-5.0	28	32	1.00 (0.63-1.58)	1.18 (0.75-1.86)
>5.0	10	13	1.15 (0.57-2.31)	1.33 (0.66-2.70)
Total	119	116		

Table 5. Number of Reported Cases and Age-Adjusted Rate Ratios (RR) for Non-Hodgkin's Lymphoma (NHL) in the Northern New Jersey Study Area, 1979-87, by Trichloroethylene (TCE) Exposure Category and Sex, All Races; NJDOH, 1993.

TCE Exposure (ppb)	Cases		Rate Ratios (95%CI)	
	Males	Females	Males	Females
a. Total Non-Hodgkin's Lymphoma (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		
b. 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		
c. Intermediate Grade NHL				
<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		
d. 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		
e. 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		
f. 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 6. Number of Reported Cases and Age-Adjusted Rate Ratios (RR) for Leukemias in the Northern New Jersey Study Area, 1979-87, by Perchloroethylene (PCE) Exposure Category and Sex, All Races; NJDOH, 1993.

PCE Exposure (ppb)	Cases		Rate Ratios (95%CI)	
	Males	Females	Males	Females
a. 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		
b. Acute Lymphocytic Leukemia (ALL)				
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		
d. Chronic Lymphocytic Leukemia (CLL)				
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		

Table 7. Number of Reported Cases and Age-Adjusted Rate Ratios (RR) for Non-Hodgkin's Lymphomas (NHL) in the Northern New Jersey Study Area, 1979-87, by Perchloroethylene (PCE) Exposure Category and Sex, All Races; NJDOH, 1993.

PCE Exposure (ppb)	Cases		Rate Ratios (95%CI)	
	Males	Females	Males	Females
a. Total Non-Hodgkin's Lymphoma (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		
b. 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		
c. 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		
d. 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		

APPENDIX A

DESCRIPTION OF POPULATION, EXPOSURE DISTRIBUTION, AND EXPOSURE-OUTCOME DISTRIBUTION

Table A1. Northern New Jersey Study Area 1980 U.S. Census Population by Age and Sex; NJDOH, 1993.

Sex	Age	Population	
		All Races	Non-white
Males	0-19	215,424	50,170
	20-49	292,180	51,788
	50-69	142,927	13,672
	70+	45,897	3,081
	Total	696,428	118,711
Females	0-19	209,012	50,164
	20-49	319,320	64,370
	50-69	166,326	17,251
	70+	78,225	5,403
	Total	772,883	137,188

Table A2. Northern New Jersey Study Area 1980 U.S. Census Population by Contamintant Exposure Category, Age, Sex, All Races; NJDOH, 1993.

Contaminant	Age	Sex	Population by Exposure Category			
a. TVOCs			≤0.1	0.1-5.0	5.1-20.0	>20.0 ppb
	0-19	Males	92,649	66,995	41,252	14,528
	20-49		124,108	88,252	56,956	22,864
	50-69		61,491	42,815	26,361	12,260
	70+		20,486	13,890	7,760	3,750
	Total		298,734	211,962	132,329	53,402
	0-19	Females	90,160	65,466	39,381	14,005
	20-49		135,348	98,005	61,466	24,501
	50-69		73,332	48,966	29,994	14,034
	70+		34,760	24,033	13,506	5,926
	Total		333,600	236,470	144,347	58,466
b. TCE			≤0.1	0.1-5.0	>5.0 ppb	
	0-19	Males	142,051	57,732	15,641	
	20-49		186,436	81,729	24,015	
	50-69		91,545	38,772	12,610	
	70+		29,057	13,058	3,782	
	Total		449,090	191,290	56,048	
	0-19	Females	138,266	55,794	14,952	
	20-49		205,170	88,502	25,648	
	50-69		106,540	45,400	14,386	
	70+		49,723	22,478	6,024	
	Total		499,699	212,174	61,010	
c. PCE			≤0.1	0.1-5.0	>5.0 ppb	
	0-19	Males	138,990	47,628	28,806	
	20-49		186,354	64,824	41,002	
	50-69		88,932	34,379	19,616	
	70+		28,071	11,508	6,318	
	Total		442,347	158,339	95,742	
	0-19	Females	135,432	45,543	28,037	
	20-49		204,645	70,518	44,157	
	50-69		103,722	39,559	23,045	
	70+		48,180	19,426	10,619	
	Total		491,979	175,046	105,858	

Table A3. Number of Leukemias in Northern New Jersey Study Area by Histological Grouping, Age Category and Sex in Each TCE Exposure Category, 1979-1987; NJDOH, 1993.

	MALES			FEMALES		
AGES	<0.1 ppb	0.1-5 ppb	>5 ppb TCE	<0.1 ppb	0.1-5 ppb	>5 ppb TCE
TOTAL LEUKEMIAS (ICD 9800-9940)						
0-19	40	16	4	29	17	7
20-49	69	18	9	39	19	10
50-69	169	67	35	96	44	17
70+	160	61	15	151	76	22
ACUTE LYMPHOCYTIC LEUKEMIA (ICD 9821)						
0-19	24	7	2	17	13	6
20-49	12	3	0	2	1	0
50-69	7	4	1	1	3	1
70+	2	2	0	5	5	0
CHRONIC LYMPHOCYTIC LEUKEMIA (ICD 9823)						
0-19	1	0	0	1	0	0
20-49	6	1	4	3	1	0
50-69	62	28	15	29	14	5
70+	56	26	6	58	25	13
ACUTE MYELOGENOUS LEUKEMIA (ICD 9861, 9866, AND 9890-9891)						
0-19	7	2	0	5	2	0
20-49	18	5	1	11	6	2
50-69	39	15	9	24	13	3
70+	39	15	5	34	19	2
CHRONIC MYELOGENOUS LEUKEMIA (ICD 9863-9864)						
0-19	1	1	0	0	2	0
20-49	14	4	1	14	3	3
50-69	25	6	4	15	7	3
70+	15	4	1	14	6	4
OTHER (ICD 9822, 9824-9850, 9862, 9865, 9870, 9880, 9910, 9930, AND 9940)						
0-19	1	0	0	0	0	0
20-49	3	1	2	1	1	0
50-69	15	6	1	7	4	0
70+	10	4	1	2	1	1
UNSPECIFIED (ICD 9800-9810, 9820, AND 9860)						
0-19	6	6	2	5	2	1
20-49	16	4	1	8	7	5
50-69	21	8	5	20	3	5
70+	38	10	2	38	20	2

Table A4. Number of Lymphomas in Northern New Jersey Study Area by Histological Grouping, Age Category and Sex in Each TCE Exposure Category, 1979-1985; NJDOH, 1993.

	MALES			FEMALES		
AGES	<0.1 ppb	0.1-5 ppb	>5 ppb TCE	<0.1 ppb	0.1-5 ppb	>5 ppb TCE
TOTAL NHL (WORKING FORMULATION GROUPS A-J: ICD 9590-93, 9600-9642, 9670-9703, AND 9750)						
0-19	17	2	0	11	4	2
20-49	81	57	21	66	34	9
50-69	235	114	35	203	84	43
70+	158	99	22	224	104	33
TOTAL LOW GRADE NHL (GROUPS A-C: ICD 9611, 9620, 9670-71, AND 9691-96)						
0-19	1	1	0	0	0	0
20-49	16	17	5	17	12	4
50-69	70	37	9	57	31	11
70+	43	22	6	45	24	6
INTERMEDIATE GRADE NHL FOLLICULAR LARGE CELL, DIFFUSE SMALL CELL, AND DIFFUSE MIXED SMALL/LARGE CELL (GROUPS D-F: ICD 9613-14, 9616, 9621-22, 9630-31, 9642, 9672-76 AND 9697-98)						
0-19	4	1	0	0	0	0
20-49	20	8	3	14	6	1
50-69	43	16	5	32	17	9
70+	26	25	4	51	16	5
DIFFUSE LARGE CELL/RETICULOSARCOMA (GROUP G: ICD 9623-24, 9632-34, 9640, AND 9680-83)						
0-19	4	0	0	1	0	1
20-49	25	14	7	13	5	1
50-69	56	29	12	41	13	8
70+	38	24	7	59	30	14
TOTAL HIGH GRADE NHL (GROUPS H-J: ICD 9600, 9602, 9612, 9641, 9684-87, 9703, AND 9750)						
0-19	4	0	0	5	1	1
20-49	5	8	1	2	4	0
50-69	6	2	2	7	1	3
70+	3	2	1	6	3	2
NON-BURKITT'S HIGH GRADE NHL (GROUPS H-J: ICD 9600, 9602, 9612, 9684-86, AND 9703)						
0-19	2	0	0	1	0	1
20-49	4	5	1	2	3	0
50-69	3	2	2	6	1	3
70+	3	2	0	6	2	2

Table A4 continued. Number of Lymphomas in Northern New Jersey Study Area by Histological Grouping, Age Category and Sex in Each TCE Exposure Category, 1979-1985; NJDOH, 1993.

OTHER NHL, NOT SPECIFIED OR NOT CLASSIFIABLE INTO GRADES (ICD 9590-93, 9601, 9610, 9615, AND 9690)

0-19	4	0	0	5	3	0
20-49	14	10	4	20	6	3
50-69	57	30	7	63	20	12
70+	47	26	4	61	29	6

MUCOCUTANEOUS LYMPHOMAS (ICD 9700-02)

0-19	0	0	0	0	0	0
20-49	1	0	1	0	1	0
50-69	3	0	0	3	3	0
70+	1	0	0	2	2	0

APPENDIX B

BASIC FACTS ABOUT LEUKEMIAS AND LYMPHOMAS

Leukemias and lymphomas are cancers of the white cells of the blood and the lymph system. In New Jersey, the average annual incidence of leukemia is about 15 per 100,000 for males and about 10 per 100,000 for females. The incidence of non-Hodgkin's lymphoma (see below) is about 15 per 100,000 for both sexes, and for lymphoma overall is 20-25 per 100,000. As a group, leukemias and lymphomas are the sixth most common cancer. For children they are the most common. (Cancer is second to accidents among the leading causes of death in children ages 1 to 14 years in the U.S.) Recognized causes of leukemias and lymphomas include genetic predisposition, smoking, and exposure to certain chemicals and radiation.

There are several broad families of blood cell types: red cells (erythrocytes), and the white cells (leukocytes) composed of lymphocytes and the myelogenous cells, monocyte/macrophages and granulocytes. Red cells carry oxygen to tissues, lymphocytes and monocyte/macrophages orchestrate immune function, while granulocytes and macrophages directly kill microbial organisms. All the white cells can migrate out of the blood and into tissues to fight infections. Mature lymphocytes reside primarily in the lymph system, especially the lymph nodes and the spleen.

In the course of normal replacement of blood cells, precursor "stem" cells in regenerative tissue in the bone marrow proliferate, with the great majority eventually differentiating into a mature blood or lymph cell. Leukemias are a group of diseases marked by abnormally proliferating bone marrow cells. Leukemic cells usually bear some degree of resemblance to one of the normal cell lineages. Most leukemias are either lymphocytic or myelogenous and are characterized as acute or chronic in their symptomatic disease development. Certain types, such as chronic myelogenous leukemia, are associated with one predominant chromosomal defect. However, there appears to

be a considerable diversity of cellular characteristics, including chromosomal defects, enzyme activities, and cell differentiation "markers", within these categories. In addition, some of these characteristics can change with progression of disease.

Lymphomas are cancers of lymphocytes, but rather than circulating in the blood, lymphoma cells congregate in the lymph system. In some cases it is not easy to differentiate the diagnosis between lymphocytic leukemia and lymphoma. Hodgkin's disease, primarily a disease of young adults, was the first lymphoma to be described. Non-Hodgkin's lymphomas (NHL) includes most of the remaining lymphomas, generally diagnosed in later adult years, and comprising a wide range of cell types. The diverse types of NHL differ in microscopic appearance, age of incidence, clinical course and response to therapy. There have been several attempts to classify NHL in a manner useful for clinical purposes and basic research. Currently, the most accepted approach is the "Working Formulation" devised by the National Cancer Institute, which groups NHL into low, intermediate, and high grades (or degrees of aggressiveness).

APPENDIX C

DISTRIBUTION OF TOWNS WITH RESPECT TO CONTAMINANT LEVELS AND WATER SOURCE

The proportions of TVOCs represented by TCE and by PCE in the 1984-1985 test data are illustrated in Tables C1 and C2. Four of the six towns with the highest levels of TCE also had the highest levels of PCE (Table C3). Conversely, only four of the eleven towns in the highest PCE category were in the highest TCE category. Three of these four towns also had detectable levels of benzene (1-5 ppb). Groundwater supplies in 1984-1985 contained most of the non-THM VOC contamination (Table C4).

Table C1. Distribution of Towns in the Northern New Jersey Study Area Towns by Trichloroethylene (TCE) vs Total Volatile Organic Compounds (TVOCs) in the Water Supply, 1984-1985; NJDOH, 1993.

NUMBERS OF TOWNS

	TVOCs (ppb)			
TCE (ppb)	<0.1	0.1-5.0	>5.0-20.0	>20.0
<0.1	29	14	5	0
0.1-5.0	0	13	8	0
>5.0	0	0	2	4

Table C2. Distribution of Towns in the Northern New Jersey Study Area Towns by Perchloroethylene (PCE) vs Total Volatile Organic Compounds (TVOCs) in the Water Supply, 1984-1985; NJDOH, 1993.

NUMBERS OF TOWNS

	TVOCs (ppb)			
PCE (ppb)	<0.1	0.1-5.0	>5.0-20.0	>20.0
<0.1	29	13	4	0
0.1-5.0	0	14	4	0
>5.0	0	0	7	4

Table C3. Distribution of Towns in the Northern New Jersey Study Area Towns by Trichloroethylene (TCE) vs Perchloroethylene (PCE) in the Water Supply, 1984-1985; NJDOH, 1993.

	NUMBERS OF TOWNS		
		PCE (ppb)	
TCE (ppb)	<0.1	0.1-5.0	>5.0
<0.1	41	5	2
0.1-5.0	4	12	5
>5.0	1	1	4

Table C4. Distribution of Northern New Jersey Study Area Towns by 1984-1985 Trichloroethylene (TCE) Category and Source of Water; NJDOH, 1993.

	NUMBERS OF TOWNS		
	TCE (1984-1985)		
	<0.1	0.1-5.0	>5.0 ppb
SURFACE WATER	22	2	0
MIXED SOURCES	2	4	3
GROUND WATER	24	12	3

APPENDIX D

RELATIONSHIP OF HISTORICAL DATA (1978-1983)

AND MANDATORY MONITORING (1984-1985)

The historical (1978-1984) data correlated well with the 1984-1985 period in that approximately two-thirds of the municipalities were in the same total non-THM VOCs category (Table D1) and the same TCE exposure category (Table D2) for both periods. Further, five of the six towns with the highest average TCE levels during the 1984-1985 period were also in the highest groups in the 1978-1983 period (Table D2). Conversely, only one town with no detected TCE during the 1984-1985 period was in the highest historical TCE category, having undergone remediation before the start of mandatory testing. Similarly, 10 of the 11 towns with the highest average PCE levels during the 1984-1985 period were also in the highest category during the 1978-1983 period, while only one town with no detected PCE during the 1984-1985 period was in the highest 1978-1983 PCE category (Table D3).

Since some water systems removed contaminated wells from service or began providing special treatment before 1984-1985, combining the historical data with the 1984-1985 data to reflect the highest average summary level of either period permitted an analysis of water supplies "ever" contaminated with TCE or PCE. There were 11 municipalities in the highest "ever-contaminated-with-TCE" category and 17 for the highest "ever-contaminated-with-PCE" category.

Between 1978 and 1985 benzene was detected in one or more samples (mostly in the 1-5 ppb range) in water supplying 26 municipalities, representing 52% of the study area population. Among most of the 26 towns, the data on benzene were less complete and consistent than for PCE and TCE. Four of the six municipalities in the jointly highest "ever" TCE and PCE categories were also contaminated with benzene, but only in one of the three towns contaminated with benzene in 1984-1985 was benzene also detected during the 1978-1983 surveys.

Table D1. Distribution of Northern New Jersey Study Area Towns by Total Volatile Organic Chemicals (TVOC) Category: 1984-1985 vs 1978-1983; NJDOH, 1993.

	NUMBERS OF TOWNS		
	TVOC (1978-1983)		
TVOC (ppb) (1984-1985)	LOW OR NONE	MEDIUM	HIGH
<0.1	16	11	2
0.1-5.0	2	18	7
>5.0-20.0	1	10	4
>20.0	0	0	4

Table D2. Distribution of Northern New Jersey Study Area Towns by Trichloroethylene (TCE) Category: 1984-1985 vs 1978-1983; NJDOH, 1993.

	NUMBER OF TOWNS		
	TCE (1978-1983)		
TCE (ppb) (1984-1985)	LOW OR NONE	MEDIUM	HIGH
<0.1	33	14	1
0.1-5.0	2	15	4
>5.0	0	1	5

Table D3. Distribution of Northern New Jersey Study Area Towns by Perchloroethylene (PCE) Category: 1984-1985 vs 1978-1983; NJDOH, 1993.

	NUMBER OF TOWNS		
	PCE (1978-1983)		
PCE (ppb) (1984-1985)	LOW OR NONE	MEDIUM	HIGH
<0.1	29	16	1
0.1-5.0	2	11	5
>5.0	0	1	10

APPENDIX E

ANALYSIS OF THE RELATIVE INFLUENCES OF TCE AND PCE

The inclusion of TCE or PCE in the analysis confounded the observed association of the other with non-Burkitt's high grade NHL among females, such that each was non-significantly associated (Table E1). This reflects the elevated incidence rate in the seven municipalities in the highest stratum of PCE contamination that are not also in the highest TCE stratum.

Analysis of the 1978-1985 data set also showed that much of the elevated incidence of childhood ALL and non-Burkitt's high grade NHL among females was attributable to the substratum of municipalities which were in both the highest "ever" TCE and PCE categories.

Table E1. The Effect of Including Perchloroethylene (PCE) Exposure Category on the Age-Adjusted Association between Trichloroethylene (TCE) Exposure Category and the Incidence of Non-Hodgkin's Lymphomas Among Females in the Northern New Jersey Study Area, 1979-1987; NJDOH, 1993.

	Rate Ratio: TCE & PCE Together	95% Confidence Interval	Rate Ratio: TCE or PCE Separately	95% Confidence Interval
b. Non-Burkitt's High Grade NHL				
TCE = <0.1 ppb	1.0		1.0	
TCE = 0.1-5.0 ppb	1.18	(0.32-4.34)	0.92	(0.36-2.37)
TCE = >5.0 ppb	2.19	(0.50-9.51)	3.17	(1.23-8.18)
PCE = <0.1 ppb	1.0		1.0	
PCE = 0.1-5.0 ppb	0.44	(0.09-2.14)	0.53	(0.15-1.82)
PCE = >5.0 ppb	1.77	(0.47-6.67)	2.74	(1.20-6.26)

APPENDIX F

ANALYSIS OF THE INFLUENCE OF CARCINOGENIC TOXIC AIR RELEASES (TRI) ON THE ASSOCIATION OF TCE WITH OUTCOME INCIDENCE

Air releases of carcinogens in the TRI database were associated with the incidence of non-Burkitt's high grade NHL among females (Table F1). The age/TRI-adjusted RR for the association of the highest 1984-1985 TCE category with non-Burkitt's high grade NHL increased from 3.17 (95%CI 1.23-8.18) to 4.72 (95%CI 1.61-13.8). Among all women, residence in towns with >30,000 lb/yr of carcinogenic releases was significantly associated with age/TCE-adjusted incidence with non-Burkitt's high grade NHL, RR = 2.78 (95%CI 1.01-7.65). Similar results were observed with the combined 1978-1985 ("ever") TCE variable.

The strength of association of TRI carcinogenic air releases with the incidence of childhood ALL among females increased in a dose-response manner. Though not statistically significant, the RR in the towns with the greatest TRI releases was 2.50 (95%CI 0.94-6.66). Including the TRI variable in the model did not affect the association with TCE. This association with TRI was diminished after analysis of the combined 1978-1985 data.

Table F1. The Effect of Including Toxic Release Inventory (TRI) Air Carcinogen Exposure Category on the Age-Adjusted Association between Trichloroethylene (TCE) Exposure Category and the Incidence of Childhood Acute Lymphocytic Leukemia (ALL) and non-Burkitt's non-Hodgkin's Lymphoma (NHL) Among Females in the Northern New Jersey Study Area, 1979-1987; NJDOH, 1993.

	Rate Ratio: TCE & TRI Together	95% Confidence Interval	Rate Ratio: TCE or TRI Separately	95% Confidence Interval
a. ALL (analysis only for under 20 years old)				
TCE = <0.1	1.0		1.0	
TCE = 0.1-5.0 ppb	2.34	(1.03-5.33)	1.90	(0.92-3.90)
TCE = >5.0 ppb	3.79	(1.41-10.2)	3.26	(1.29-8.28)
TRI = <0.1	1.0		1.0	
TRI = 300-3,000 lb/yr	0.90	(0.28-2.86)	1.23	(0.42-3.72)
TRI = 3,000-30,000 lb/yr	1.42	(0.59-3.40)	1.15	(0.50-2.67)
TRI = >30,000 lb/yr	2.50	(0.94-6.66)	1.72	(0.71-4.15)
b. Non-Burkitt's High Grade NHL				
TCE = <0.1	1.0		1.0	
TCE = 0.1-5.0 ppb	1.36	(0.47-3.89)	0.92	(0.36-2.37)
TCE = >5.0 ppb	4.72	(1.61-13.8)	3.17	(1.23-8.18)
TRI = <0.1	1.0		1.0	
TRI = 300-3,000 lb/yr	0.68	(0.16-2.85)	1.44	(0.40-5.154)
TRI = 3,000-30,000 lb/yr	1.20	(0.40-3.58)	1.33	(0.46-3.83)
TRI = >30,000 lb/yr	2.78	(1.01-7.65)	2.17	(0.84-5.61)