WOBURN CHILDHOOD LEUKEMIA FOLLOW-UP STUDY

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EXECUTIVE SUMMARY

Woburn, Massachusetts, is a community of approximately 35,000 people, located 13 miles northwest of Boston. It has an extensive industrial history spanning over 130 years which included greenhouse operation, leather manufacturing and chemical manufacturing. Products manufactured included arsenic compounds used in pesticides, textiles, paper, TNT, and animal glues. The deposition of hazardous material and waste products from these industries has been a long-standing point of environmental concern for citizens and government officials.

In 1979, environmental concerns were brought to the forefront of public attention when excavation of a former industrial site unearthed significant amounts of industrial waste that proved to be contaminated with high levels of lead, arsenic, and heavy metals. It was subsequently learned that two municipal drinking water wells which had been installed near this site were contaminated with trichlorethylene (TCE), perchloro-ethylene, chloroform and other organic compounds. These wells had supplied public water primarily to the eastern portion of Woburn between 1964 and 1979.

Woburn residents were concerned regarding health effects that may have resulted from consumption of the contaminated water. These concerns were heightened when it was learned that between January 1969 and December 1979, twelve cases of childhood leukemia had been diagnosed in Woburn, six of these cases resided in a six-block area which was served directly by the contaminated wells. Identification of these cases prompted the Massachusetts Department of Public Health (MDPH) and the Centers for Disease Control (CDC) to begin a formal investigation of the health status of Woburn residents.

Results of a case-control investigation conducted by MDPH were published in January 1981. The investigation concluded: (1) the incidence of childhood leukemia was significantly elevated in Wobum (12 observed cases vs. 5.3 expected cases between 1969 and 1979); (2) the majority of the excess cases were males; and (3) six of the cases were diagnosed while residing in a single census tract in Woburn. At the time, the cases in this census tract represented half the identified childhood leukemias, a number disproportionate to the geographic distribution of the population in the community. In 1984, the MDPH released a summary report which identified an additional seven cases diagnosed through 1983 and demonstrated a continued excess in the incidence of childhood leukemia (19 observed cases vs. 6. 1 expected).

By the middle of 1986, a total of 21 childhood leukemia cases had been diagnosed in Woburn. Cases diagnosed after 1979 had birth residences, which were more evenly distributed throughout Woburn than the original 12 cases. As a result of

the continued elevated incidence and the change in the geographic distribution of the cases, MDPH conducted the Childhood Leukemia Follow-Up Study.

Study Design

The study is a matched case-control design with two controls selected for each case. All cases were children 19 years of age or younger and diagnosed with leukemia between 1969 and 1989 while residents of Woburn. Controls were selected randomly from Woburn school records and matched to cases based on date of birth (plus or minus 3 months), sex and race. Controls must have been Wobum residents at the time of diagnosis of the matched case. Residential, occupational and health history data were collected during interview for the etiologic period for each case and its matched controls. The etiologic period is defined as the period of time from two years before conception to the case's leukemia diagnosis and is sub-divided for analysis into the time segments two years before conception to conception, during pregnancy, and from birth to case diagnosis.

Results

Univariate Analyses

Detailed analyses of data collected at interview revealed five variables for which 10 or more total positive responses were identified and that demonstrated odds ratios greater than or equal to 1.50 in relation to the childhood leukemia incidence.

Maternal alcohol consumption during pregnancy (O.R- = 1. 50, C.I. = 0. 54, 4.20); diagnosis of a paternal grandfather with cancer (O.R- = 2.01, C.I. = 0.73, 5.58); having a father
who worked for industries considered high risk for occupational exposures (O.R- = 2.50, C.I. = 0.78, 8.30); and the subject's consumption of public water as their primary beverage (O.R- = 3.03,C.I. = 0.82, 11.28) were all variables which showed non-significant but positive associations with childhood leukemia incidence. A statistically significant association was identified between developing childhood leukemia and being breast-fed as a child (O.R- = 10. 17, C.I. = 1.22, 84.58).

Multivariate Analyses and Exposure to Wells G and H

Multivariate analyses of the relationship between childhood leukemia and exposure to water from Wells G and H revealed that although five variables discussed above showed elevated odds ratios as univariates in relation to the leukemia, they did not significantly affect odds ratios specific to water exposure. Adjusted odds ratios were calculated controlling for socioeconomic status, maternal smoking during pregnancy, maternal age at birth of the child, and maternal alcohol consumption during

pregnancy. Of these variables, only maternal alcohol consumption during pregnancy demonstrated a slightly elevated odds ratio in univariate analyses. The literature suggests, however, that these variables are suspected to be associated with leukemia incidence or adverse reproductive outcomes and were, therefore, kept in the model as part of the primary analysis.

Adjusted odds ratios describing the effects of Wells G and H water on leukemia incidence showed a non-significant elevation for the overall etiologic period (O.R- = 2.39, C.I. = 0.54, 10.59) and each time period subcategory. The strongest relationship between exposure and leukemia among time period subcategories is during pregnancy (O.R- = 8.33, C.I. = 0.73, 94.67), the second is in the two years before conception (O.R- = 2.61, C.I. = 0.47, 14.37) and the weakest is in the time period between the birth of the case and the diagnosis of leukemia (O.R- = 1.18, C.I. = 0.28, 5.05).

Sub-stratification of the pregnancy time period to assess specific effects of water exposure by trimester revealed high correlation coefficients between trimester exposure values. Independent effects of water exposure by trimester on leukemia incidence could, therefore, not be distinguished with confidence.

Analyses to assess potential dose response relationships were completed using a trichotomous parameterization of the actual study subject exposure values by time period. Results demonstrated elevated odds ratios between dose categories for the preconception and pregnancy periods. A significant trend across exposure categories was also identified for the period during pregnancy ($P < 0.05$) suggesting a dose-response relationship for subjects whose mothers drank Wells G and H water during pregnancy. Tests for trend for the etiologic period overall and for each of the other time period subcategories were not significant ($P > 0.05$).

Discussion and Conclusions

This finding suggests that the relative risk of developing childhood leukemia was greater for those children whose mothers were likely to have consumed water from Wells G and H during pregnancy this association showed a significantly positive relationship to the amount of water households received. Further research in other populations is necessary to definitively address this trend and examine potential embryologic windows of increased vulnerability to leukemogens. In contrast, there appeared to be no association between the development of childhood leukemia and consumption of water from Wells G and H by the children prior to their diagnosis.

Few positive associations were identified between childhood leukemia incidence and residential parental occupation, and medical history related risk factor information

collecting during interview. A statistically significant relationship was identified between breast feeding and childhood leukemia, although a mechanism for this relationship is unclear.

The literature demonstrates that certain chemical exposures have been associated with health effects in both children and adults. TCE, one chemical detected in the well water, is known to have weak hematologic effects in mammals but no effect on humans in studies thus far, although effects on the developing human fetus are unclear. The nature and extent of historical contamination of Wells G and H is not known. However, in our study, it seems the exposure, whether multichemical or specific in nature, may have had an effect on blood-forming organs during fetal development, but not during childhood.

The small number of study subjects lead to imprecise estimates of risk. As a result, the exact magnitude of the association between exposure to water from Wells G and H and risk of childhood leukemia cannot be stated. Results, however, demonstrate consistency in the direction of an association, suggest a dose-response relationship and demonstrate a decrease in effect after the elimination of the potential for exposure. We conclude that the incidence of childhood leukemia in Wobum between 1969 and 1989 is associated with mothers' potential for exposure to contaminated water from Wells G and H, particularly for exposure during pregnancy.

INTRODUCTION

The purpose of this investigation, as proposed in November 1987, was to provide further insight into the causes of childhood leukemia among persons nineteen years of age or younger who were diagnosed with leukemia between January 1, 1969 and August 31, 1989 and were residents of Woburn at the time of their diagnosis. No new childhood leukemia cases were diagnosed, however, until early in 1994. This work serves to supplement previous efforts of the Massachusetts Department of Public Health (MDPH) (Parker and Rosen, 1981) (Friede, 1984) which confirmed the increased incidence of childhood leukemia in Woburn.

The objective of this study was to re-analyze the original data set by obtaining more complete information for the twelve childhood leukemia cases included in the 1981 investigation and to expand the study to include the additional 9 cases diagnosed as of August, 1989. This investigation has utilized more refined scientific methods for exposure assessment made available during the Woburn Environment and Birth Study and information regarding potential causes of cancer not available at the time of the original MDPH study. It directly evaluates the relationship between exposure to water from Wells G and H and childhood leukemia incidence and how other potential risk factors may have contributed to the increased incidence.

BACKGROUND

Statement of the Problem

The City of Woburn, Massachusetts is located approximately 13 miles northwest of Boston. It has been an industrial community for over 130 years hosting a variety of industries including greenhouses, leather manufacturers and chemical manufacturers producing products such as arsenic compounds for insect control, textiles, paper, TNT, and animal glues.

Complaints by citizens regarding water quality and ambient air odors date back for over 100 years.

In the spring and summer of 1979, attention was drawn to environmental hazards in Woburn when excavation in an 800 acre industrial area of the city revealed substantial hazardous wastes. Abandoned lagoons severely contaminated with lead, arsenic, heavy metals and buried animal hides were unearthed on the site commonly known as Industri-Plex. The unearthed hides released high levels of hydrogen sulfide and methane gas that spread the familiar Woburn odor to surrounding communities. The issue drew public attention when toxic waste disposal at the town dump was revealed and when municipal drinking water testing indicated the presence of contamination in two wells. City Wells G and H were found to be contaminated with trichloroethylene (TCE), perchloroethylene, chloroform, and other organic compounds. The wells were first used in 1964 but were shut down by the Department of Environmental Quality Engineering (DEQE, now the Department of Environmental Protection (DEP)) in 1979 when the contamination was discovered. They had been used to supplement Woburn's public water supply particularly in East Woburn.

Woburn residents, having become concerned regarding possible ill health effects the contamination may have caused, became alarmed when they identified twelve cases of childhood leukemia in the community that had been diagnosed between January 1969 and December 1979. The Centers for Disease Control (CDC) also received a report from a Boston pediatric hematologist stating that he had identified six of these cases in a six block area of Woburn. These events prompted the Massachusetts Department of Public Health (MDPH) and the CDC to begin a formal investigation of the health status of Woburn residents.

A report was published by MDPH in January 1981 entitled "Woburn Cancer Incidence and Environmental Hazards, 1969-1978". It outlined the results of the MDPH/CDC case-control study which concluded: 1) the incidence of childhood leukemia was significantly elevated in Woburn (12 observed cases vs. 5.3 expected cases); 2) the majority of the excess cases were males, and 3) six of the cases were diagnosed while residing in a single census tract in Woburn. At the time, the cases in this census tract represented half the childhood leukemias, a number disproportionate to the geographic distribution of the population in the community.

In November of 1981, MDPH released a second report entitled "Cancer Mortality in Woburn, A Three Decade Study (1949-1978)." This report reviewed trends in leukemia mortality before, during, and after the use of the contaminated wells. It concluded that childhood leukemia mortality was not elevated during the period between 1949 and 1958 but began to rise between 1959 and 1963. No unusual geographic distribution of childhood leukemia mortality occurred during the period from 1949 to 1968.

In February of 1984, Harvard researchers published the results of a study they conducted in Woburn during 1982 (Lagakos, 1986) to address the childhood leukemia concerns and to examine other health outcomes as well. Harvard researchers were interested in determining if elevations in childhood leukemia incidence rates remained elevated beyond 1979, after the original MDPH report. The researchers also wished to further investigate the relationship between the incidence of childhood leukemia and the availability of water from Wells G and H.

Their analysis included 15 childhood leukemia cases who were born during the period 1960 to 1972 and were residents of Woburn at the time of diagnosis. The 15 cases included 11 of the 12 original MDPH cases. One MDPH case born before 1960 was excluded, and four

other cases diagnosed in Woburn between 1980 and 1982 were added. They determined that Woburn's childhood leukemia rate continued to be elevated through 1982.

The Harvard researchers administered a telephone survey questionnaire to 3257 households in Woburn between April and September 1982. The questionnaire was designed to yield additional data for the determination of an association between the contaminated water and childhood leukemia. A water distribution simulation model prepared by the DEQE, now the DEP, was used to provide information concerning the amount of mixing of public water from different sources and its distribution to homes throughout Woburn. The DEQE study estimated on a monthly basis which of five identified zones of graduated exposure received none, some, or all of their water from Wells G and H.

Researchers then estimated the percentage of each household's annual water supply that arose from Wells G and H. The data was used to assign to each subject a cumulative exposure score beginning with the annual exposure score corresponding to the mother's residence in the year the pregnancy ended. The child's individual score would be the sum of the scores for each year of their Woburn residence within the study period. If a child changed residences, the child's score for that year was arbitrarily defined as the score corresponding to the former residence. (Lagakos, 1986).

The Harvard study determined positive associations between water use from the contaminated wells and the risk of childhood leukemia, prenatal death (post 1970), lung/respiratory disorders, kidney/urinary disorders, eye/ear birth defects, and "environmental" birth defects- an arbitrarily constructed grouping of those birth defects that reportedly have been linked in the scientific literature with external environmental factors such as chemicals, pesticides, radiation, or trace elements in water. The study recommended that town and state

health departments consider initiating a long-term health surveillance system for the monitoring of childhood and reproductive disorders.

In 1984, as a result of the availability of cancer incidence data from the newly created Massachusetts Cancer Registry, MDPH released updated information concerning Woburn childhood leukemia incidence (Memorandum from A. Friede to J. Cutler, 1984). They confirmed seven new cases since the release of their January 1981 study that included three new cases since the Harvard Study was completed. The total number of childhood leukemia cases was then nineteen.

Geographically, the seven new cases were distributed more randomly throughout the city than the original twelve and were not limited to the areas supplied by the contaminated wells. Analysis of the entire group of cases diagnosed through 1983 revealed a continued leukemia excess than at the time of the original investigation. Three census tracts now showed a significant elevation in incidence as opposed to only one census tract originally.

As a result of this continued trend, MDPH with financial support from the CDC drew together an advisory panel comprised of experts in the field of epidemiology, prenatal epidemiology, toxicology, environmental engineering, genetics, medicine, statistics, sociology, and virology. The Woburn Advisory Panel reviewed the studies and background information to date and provided recommendations (Woburn Advisory Panel, 1985) to MDPH. Among its recommendations the expert panel suggested "a closer investigation of incident cases of childhood leukemia and their families in the continuing search for etiologic clues."

Between 1986 and August 1, 1989, two additional cases were diagnosed for a total of twenty-one childhood leukemias identified as having been diagnosed in children up to nineteen years of age between 1969 and 1989. The cases belonged to three of the four histopathological

types of leukemia. Seventeen cases have been identified as acute lymphocytic leukemia (ALL), 3 cases as acute myelocytic leukemia (AML) and 1 case as chronic myelocytic leukemia (CML). None of the children were reported as having the fourth major histopathologic type, chronic lymphocytic leukemia (CLL).

Leukemia cases diagnosed after 1979 had birth residences that appeared to be more evenly distributed throughout Woburn than previous cases, suggesting that factors other than geographic area of residence may be related to leukemia incidence. In order to examine the leukemia incidence more closely, MDPH decided to expand their 1981 analysis by re-examining the twelve cases they studied originally and adding the more recently identified cases to their analysis. The Woburn Childhood Leukemia Follow-Up Study included the twenty-one cases of childhood leukemia reported to the MDPH from hospitals or the Massachusetts Cancer Registry as having been diagnosed between January 1, 1969 and August 31, 1989.

The Woburn Advisory Panel also suggested the establishment of a surveillance system to monitor the frequency of selected reproductive outcomes in Woburn as an indicator of potential health effects the environmental exposures may be having on the community. In response, the Massachusetts Department of Public Health and the U.S. Centers for Disease Control and Prevention formed a cooperative agreement in order to complete the Woburn Environment and Birth Study (WEBS) (1994). The WEBS study found that, in general, birth defect rates in Woburn were no different from the rates for the twelve communities surrounding Woburn for the study period.

History of Wells G and H Municipal Water Supply

History of Woburn's Water Supply

The City of Woburn has had a long history of problems with water quality, as well as an inadequate volume of water. Documented water supply problems date back to the late 1800's, persisting through May 1979. Although May 1979 coincides with the date that the Massachusetts Department of Environmental Protection (MA DEP) advised that the water from Woburn's Wells G and H should not be used for public water supply purposes (McCall, 1979), the history of water quality problems more directly relates to Woburn's various industrial activities and the pollution of aquifers that underlie the City, as well as pollution of the Aberjona River running through Woburn.

During the period 1871-1911, the prime sources of pollution of the Woburn sections of the Aberjona River and its tributaries were the tanneries, leather-related industries, and chemical industries. From 1911 through 1956, tannery pollution and chemical wastes continued as the major sources of surface and groundwater contamination, impacting upon City sewerage systems. The period 1956 through 1984 was marked by the development and discovery of additional water pollution sources by a variety of firms conducting other forms of industrial activity, (Tarr, 1987).

In 1955 the City of Woburn contracted with Whitman and Howard, Inc. to conduct a study of the Woburn water system and recommend improvements (Tarr, 1987). Contained in that report was a reference to the use of the Aberjona River Valley (Aberjona Aquifer) as a source of public water supply. This report states, "the Aberjona River Valley still has a potential for groundwater supply for certain industrial uses, but the groundwater of this valley are, in general, too polluted to be used for public water supply," (Whitman and Howard, 1958). Despite this warning, increased demands on the town's water supply by the mid-1960s led to the

digging of test wells at various sites in the Aberjona Aquifer, including Wells 15 and 16, later to become Wells G and H, respectively (Tarr, 1987).

Wells G and H were put into service during the 1960's as supplementary water sources. Well G began pumping in October of 1964 and Well H began pumping in the first half of 1967 (Tarr, 1987). They were in service for 2995.5 days, representing a little more than half of the total days of their period of operation. The Wells drew water from the Aberjona River Aquifer and provided approximately 24% of the City's water supply (Special Legislation Commission on Water Supply, 1986). Woburn's other municipal supply wells drew water from the Horn Pond Aquifer.

Throughout the Wells G and H period of operation, there are repeated references (1964 through 1977) to the poor quality of the water pumped from the Wells, including reports of elevated levels of nitrates, ammonia, nitrogen, chlorides, sulfates, sodium, manganese, iron, and a reference as early as 1964 to the "presence of some organic materials" (Tarr, 1987). Other complaints by residents included bad taste, odors, color and staining of plumbing fixtures and laundry. Some residents reported that they could tell when the Wells were in service because of the marked change in water quality. MA DPH, in 1975, advised the City to seek an alternative water supply due to the poor aesthetic water quality.

The discovery of nearby toxic wastes in 1979 led to the testing of Wells G and H for chemical contaminants by the MA DEP. Trichloroethylene (267 ppb) and tetrachloroethylene (21 ppb) were found to exceed drinking water guidelines. Low levels of chloroform, methyl chloroform, trichlorotrifluoroethane, 1,2-dichloroethylene and inorganic arsenic were also detected. As a result of these tests, Woburn's Wells G and H were closed in May, 1979.

Today, the Massachusetts Water Resource Authority provides 40% of Woburn's water and the remaining 60% of Woburn's water supply is drawn from the Horn Pond Valley from gravel wells on the westerly and southerly shores of the pond. Woburn's Horn Pond water supply system is possibly the oldest municipal system in Massachusetts (verbal communication, City of Woburn Pumping Station personnel, 1992).

Contamination of Wells G & H

Documents developed by the United States Environmental Protection Agency (US EPA), the MA DEP, and their consultants provided information on groundwater contamination and the industries that were responsible for contaminating Wells G and H. The MA DPH conducted a Wells G and H Health Assessment in 1989, in collaboration with the Agency for Toxic Substances and Disease Registry (ATSDR), to evaluate the public health implications associated with the levels of contamination detected in Wells G and H, the contaminated groundwater within the area of influence of Wells G and H, and the contaminants found in various media in and around what has come to be known as the Wells G and H National Priority List (NPL) site (Wells G and H, 1989).

Five properties within the Wells G and H site have been determined to contain soil contamination and contributed to the contamination of groundwater in the vicinity of Wells G and H. These properties ranged in distance from 200 to 2300 feet to the wells.

It was not possible to establish when chemical contaminants first reached the Wells, nor the degree to which concentrations of various chemicals may have varied over time. It was possible, however, to examine the known hydrology of the area and contaminated groundwater plumes and it was deemed plausible that contaminated groundwater reached Wells G and H prior to 1979.

For the purposes of this study, it was assumed that the chemical substances determined to be of concern to public health and detected in the groundwater at the five properties presumed to be responsible for contaminating Wells G and H had, in fact, reached the wells prior to 1979. These chemical substances include trichloroethylene, tetrachloroethylene, trans-1-dichloroethylene, arsenic, lead, chlordane, 1,1,1-trichloroethylene, chloroform, methyl chloroform, and vinyl chloride.

REVIEW OF THE LITERATURE

Pathophysiology

Leukemia literally means "white blood" -- a reference to the excessive numbers of leukocytes (or white blood cells) in the peripheral blood of leukemics. The serious symptoms of the disease, however, are caused by a lack of normally functioning cells and/or platelets; this deficiency is brought about through proliferation of cells that resemble a stage in normal blood-cell development but which are incapable of performing the functions of mature blood cells [Miller et al., 1986; Clarkson, 1980] such as fighting off foreign invaders to the body by attacking them (the function of some granulocytes and the "T" lymphocytes) or releasing harmful substances (the function of some granulocytes and the "B" lymphocytes).

The transformation from normal precursor to leukemic cell can occur at various points along the developmental pathways of the granulocytes and lymphocytes [Clarkson, 1980]. Conditions referred to as "acute" leukemias result from early transformations which leave cells blocked at an immature stage. Different acute leukemias are distinguished by the type of immature cell that is found in the peripheral circulation (where mature cells are needed). The most common form of leukemia affecting children (80 percent of childhood cases [MacMahon,

1992a]) is acute lymphoblastic (or lymphocytic) leukemia (ALL), in which lymphoblasts fail to develop into lymphocytes and accumulate. It is important to recognize that adult ALL and childhood ALL may be distinct entities. Although Doll [1989] has stated that the distinction between childhood and adult leukemia is not absolute, Schull, et al. [1988] considers differences between childhood and adult cases in terms of cell types, chromosomal markers, and response to therapy as indications of the involvement of different cellular and molecular events at different ages. Even childhood ALL is heterogeneous in that any of three different types of lymphoblasts may constitute the abnormal species in a particular case [Cresanta, 1992]. Accumulation of B lymphoblasts (a feature of 90% of childhood ALL cases [Doll, 1989]) characterizes the disease as it occurs in young children [Kaye et al., 1991]. T lymphoblasts, on the other hand, accumulate in the blood of older childhood ALL victims [Kaye et al., 1991].

When myelocytes, which normally develop into granulocytes, are found in the peripheral blood, the condition is referred to as acute myelocytic leukemia (AML). AML also occurs in children; however, it is only about one-fifth as common as ALL in this period, occurring at a rate of eight cases per million in infancy, as compared to 38 cases of ALL per million in children under the age of five [Linet, 1985].

It is worthy of note that, if the leukemic transformation occurs in one or a few cells, as is believed [Clarkson, 1980], the potential remains for the production of normal cells as well. Eventually, though, the normal precursors to all blood cells are greatly reduced through an inhibitory effect of the leukemic cells or their products [Clarkson, 1980; Linet, 1985; Miller et al., 1986] such that the untreated patient is threatened by hemorrhage, infection, and inadequate cellular nutrition [Miller et al., 1986].

The chronic leukemias are so called because the duration of these forms tends to be longer, although remissions are achieved through medical treatment in all types of leukemia [Smith, 1986; Clarkson, 1980]. Chronic lymphocytic leukemia (CLL) is unheard of in children [Draper et al., 1993], and the rate of chronic myelogenous leukemia in children and young adults is only two cases per 1,000,000 population [Linet, 1985]. Due to the rarity of chronic leukemia in children, these forms will not be discussed.

Latency

As with other forms of cancer, latency is a feature of the natural history of leukemia. "Latency" refers to the tendency for a disease to first become evident long after the underlying malignant process has begun. "Induction period," a related term, is the time between first exposure to the cause of interest (and, of course, there are likely to be multiple causes for any case of cancer) and the start of the disease process. Neither latent periods (defined here as the time between disease onset and detection) nor induction times can be measured; we must be satisfied with knowing the length of the empirical induction time -- the time between the occurrence of the exposure of interest and the detection of signs of disease.

Comparatively speaking, empirical induction times for leukemogenic agents are shorter than those observed for other types of cancer [Land and Norman, 1978; Smith and Doll, 1978]. Leukemia occurred in survivors of atomic bomb blasts in Hiroshima and Nagasaki from two to thirty years after exposure [Heath, 1982; Ohkita et al., 1978; Shore, 1989]. In this population, some evidence has accrued of a negative relationship between amount of radiation and induction time [Land and Norman, 1978]; generally speaking, though, shorter induction times were observed for younger victims [Heath, 1982]. Children exposed in utero to diagnostic X-rays, however, developed leukemia at between ten and 15 years of age [Stewart and Kneale, 1970].

Furthermore, recently completed cluster investigations demonstrated clustering of births for older-diagnosed cases and clustering of residences occupied near the time of diagnosis for younger diagnosed cases. These data tend to indicate that, even among children, younger age at exposure may be associated with shorter latency.

Survival

It is important to recognize that, despite progress over the past ten to fifteen years in the chemotherapeutic induction of remissions from leukemia [Miller et al., 1986; Clarkson, 1980], it remains a very serious disease. Complete remission implies no leukemic cells in either the bone marrow or peripheral blood [Miller et al., 1986], but relapses are common, such that the term "complete remission" should not be confused with cure. Also, because acute leukemias are generally fatal if untreated [Clarkson, 1980], therapeutic interventions tend to be aggressive and involve hospitalizations and long-term administration of maximally tolerated doses of highly toxic drugs [Miller et al., 1986]. With such treatment, 90 percent of the victims of pediatric ALL (a disease that was almost universally fatal prior to 1965 [Pratt et al., 1988]) go into complete remission, and today, 72 percent of this group achieves long-term leukemia-free survival [American Cancer Society, 1993]. The five-year survival rate is much higher for ALL than for AML, however [Page and Asire, 1985].

Descriptive Epidemiology of Childhood Leukemia

Incidence

Fewer than 10,000 cases of all types of cancer combined are diagnosed in American children each year [Tarbell et al., 1986]; however, a large percentage of these are leukemias. According to the American Cancer Society [1993], 2,600 children in the U.S. will have been

diagnosed with leukemia in 1993 and ALL, which occurs at an average annual rate of 32 cases per million children under age 15 [Kaye et al., 1991], will be the specific diagnosis of 2,000 of these.

Mortality

Mortality from childhood cancer in general has decreased steadily from 90 deaths per million children in 1950 to 50 per million in 1978 [Li, 1982] to 40 per million in 1989 [American Cancer Society, 1993].

Age and Sex

AML occurs at a constant low rate throughout early childhood, the annual incidence rising sharply between the mid-teens and mid-twenties to about five to ten cases per million. ALL shows a strikingly different pattern; peak incidence (around 40 cases per million [Linet, 1985]) occurs between ages one and four, and incidence decreases rapidly to a low of only about one case per million population annually at around age 30 [Linet, 1985]. In childhood, leukemia occurs only slightly more often in males versus females (sex ratio = 1.2 to 1.0 [Doll, 1989]), and the age patterns for the two sexes are similar [MacMahon, 1992a].

Race and Geography

Doll [1989] reports that, when certain outliners are excluded, the range in incidence of all childhood cancers worldwide is quite narrow (31 to 49 cases per million population). The notable exceptions are Africa, Fiji, and some parts of Asia, where incidence ranges between 10 and 20 cases per million. Black populations everywhere also exhibit low incidence; childhood leukemia was found to be diagnosed only half as frequently in black children versus white children by the Third National Cancer Survey [Li, 1982].

Interestingly, where incidence is low, the early childhood peak in ALL incidence is also missing [Doll, 1989]. This difference could well be due to detection bias resulting from decreased medical attention received by black children versus white children. Reports of low leukemia incidence have been noted in parts of Africa with "good medical facilities and well-trained hematologists," leading them to conclude that childhood leukemia actually occurs less frequently in black populations versus white.

In a California study, Shaw et al. [1984] found a statistically significant association between having a Spanish surname and leukemia registrations -- a finding that was unaffected by restriction of analyses to residents of an area with complete reporting. The racial mixture of controls was representative of the underlying population.

Socioeconomic Status (SES)

Results of some studies of childhood leukemia have suggested an association with high socioeconomic status (SES) [Shaw et al., 1984, Ramot and Magrath, 1982; Van Steensel-Moll et al., 1986; Lancet editors, 1990]. However, the link has recently been described as "modest" [Alexander et al., 1990a] and "weak" [MacMahon, 1992a], and some researchers have failed to find it at all [Shaw et al., 1984].

Knox et al. [1984] suggested that the leukemia-SES association reflects a greater tendency of high-SES children versus low-SES children to survive the infectious diseases of infancy and early childhood. The weakening or disappearance of the leukemia-SES association with time might be explicable in these terms, considering the secular decrease in infant death rates due to infection.

Maternal Age/Birth Order

Children with Down Syndrome have higher rates of leukemia than do unaffected children. Since Down Syndrome is related to maternal age and is believed to result from genetic changes occurring during egg-cell division, researchers have looked for evidence of a link between advanced maternal age and childhood leukemia in the hope of identifying a similar etiologic mechanism. The conflicting conclusions of the relevant research led Shaw et al. [1984] to test this hypothesis in a case-control study. These authors interpreted their results negatively, however. Cases were found to be 2.29 times as likely as controls to have been born to a woman aged 40 or older. This difference was not statistically significant, but only 15 subjects altogether had mothers in this age range. Kaye et al. [1991] found a similar (and significantly elevated) odds ratio when they compared the leukemia risk of children born to mothers who were 35+ years old to that of those who were younger.

Researchers have also disagreed on the relationship between birth order and childhood leukemia incidence, with some investigators reporting that firstborn children are at higher risk [Van Steensel-Moll et al., 1986; Roman et al., 1993] while others have found higher risk associated with later birth orders [Shaw et al., 1984]. An interesting new finding reported by Kaye et al. [1991] concerns an association between leukemia risk and the number of years between one's birth date and that of his/her next older sibling.

Clustering

No discussion of the epidemiology of childhood leukemia would be complete without some exploration of its reputation as a disease that occurs in clusters. Most simply defined, clustering is the close occurrence in time and space of different cases of a particular disease. If

the disease in question were infectious, we would refer to a cluster as an "epidemic." By extension, we could say that a cluster is a non-infectious disease epidemic.

The significance that has been attached to clustering derives from its resemblance to a feature of infectious-disease epidemiology, such that it has been taken by some as evidence that childhood leukemia has an infectious cause. There are reasons to suspect an infectious etiology for childhood leukemia, but it would be naive either to consider clustering as proof of an infectious etiology or to interpret a lack of clustering as strong evidence against an infectious origin. Any disease related to the environment would tend to cluster geographically, as would any disease related to host factors if the affected hosts tended to cluster geographically. Furthermore, although the absence of clustering could imply that disease occurrence is entirely random, it could also mean that the risk factors are so evenly distributed across the population that associations aren't discernible [Mathews, 1988].

Etiologic Hypotheses

In 1987, Sandler and Collman, referring to leukemia, wrote that "despite the extensive literature devoted to the subject, little has been learned about risk factors for the disease." These authors' conclusions related to adult leukemias, but Cartwright [1989] recently identified risk factors for childhood ALL as "neonatal x-ray exposure, lack of vaccination and possible unusual patterns of infection, chloramphenicol use and very little else." Actually, Sandler and Collman [1987] question the connection between chloramphenicol use and leukemia, because the case-report data have not been supported by experimental studies or by follow-up of patients with chloramphenicol-induced bone marrow depression. Case reports have also implicated phenylbutazone and cancer-chemotherapy drugs in non-lymphocytic leukemia causation. Animal data have confirmed the association in the case of the anti-neoplastic [Sandler and

Collman, 1987]. Linet [1985] suggested further study for phenylbutazone, because, although results of analytic studies had been negative, only two such investigations had been completed by 1985.

Benzene

Both Linet [1985] and Austin et al. [1988] have reviewed the literature linking benzene to leukemia. In introductory comments, the latter group of reviewers states that benzene is widely considered to be a human leukemogen. Declining to consider the animal investigations (though they do note that limited evidence of a carcinogenic effect has recently been strengthened by further study), these authors identified fourteen epidemiologic investigations concerning benzene and leukemia. Of the eleven papers published since 1977, five found significant associations between benzene exposure or high benzene exposure and leukemia, and in five, a positive but non-significant association was reported. Two of this latter group were case-control studies based on very small numbers of cases (eleven and fifteen). The remaining retrospective investigation was hospital based and relied on medical records to evaluate exposure status (exposed versus not exposed). Only seven exposed patients were identified.

Other Solvents

Lowengart et al. [1987] performed a case-control study of children aged 10 years and under in Los Angeles County to identify causes of acute leukemia. Analysis of 123 matched pairs showed an increased risk of leukemia for children whose fathers were occupationally exposed to certain chemicals after their birth. Results showed effects with chlorinated solvents (OR = 3.0, p = 0.05), spray paint (OR = 2.0, p = 0.02), dyes (OR = 3.0, p = 0.05, and cutting oil (OR = 1.7, p = 0.05). An elevated rate was also seen when a father was exposed to spray paint

during the mother's pregnancy. There was an increased risk for the child where parents used pesticides in the home (or = 3.8, p = 0.004) or garden (OR = 6.5, p = 0.007).

Tobacco

Linet [1985] states that there is no evidence of a strong association between the leukemias and tobacco use. She goes on to cite relative risks in the range of 1.5 from several large prospective studies. A relative risk of 1.5 implies that the leukemia risk of smokers is one and one half times that of nonsmokers. Relative risks under 2.0 are said to indicate weak associations, and, unless demonstrated repeatedly in well designed studies, are considered suspect, because they may be accounted for by uncontrolled "confounders." Confounders are exposures or attributes which, through their association with both the exposure under investigation and the outcome of interest, make it appear as though a causal relationship exists between the supposed risk factor and the disease in question [Wald, 1988].

Sandler et al. (1993) reported in the results of a case-control study conducted with over 600 leukemia cases that smoking was associated with a modest increase in leukemia risk overall (O.R. = 1.13, 95% C.I. = 0.89, 1.44). Researchers found, however, that among participants aged 60 and older, smoking was associated with a twofold increase in the risk of acute myeloid leukemia (AML) (O.R. = 1.96, 95% C.I. = 0.97, 11.9). No overall association between smoking and leukemia among younger persons was identified. Among a subset of younger patients there were associations between smoking and leukemia for patients with similar morphologic and cytogenic features as the older cases.

Viruses

There are numerous reasons to believe that infectious agents cause leukemias. First and foremost, perhaps, is the certainty of their role in animal leukemia [Heath, 1982]. Retroviruses,

which contain RNA as their genetic material [Davis et al., 1980], cause leukemia in cows, cats, chickens, gibbons, birds, and primates. The viruses can be transmitted in various bodily fluids, and leukemia follows infection by months or years [Linet, 1985]. The observation that leukemia viruses cross species [Linet, 1985] barriers has perhaps fueled the search for evidence of transmission of animal leukemia viruses to humans.

60 Hz EMF

In recent years a public health controversy has arisen concerning health effects and exposure to extremely low frequency electric and magnetic fields (EMFs) produced by electrical fixtures which produce, deliver, or use electricity. "EMF" is a general abbreviation for electric and magnetic fields that are produced in all ranges of the electromagnetic spectrum. "EMF" has commonly come into use in reference to extremely low frequency electromagnetic energy that is sometimes abbreviated as ELF. This type of energy is produced by 60 Hertz (Hz) electric power, the form of electricity carried by power lines and used in homes, offices, and factories. Electric fields are produced by the presence of electric charges measured as voltage. Magnetic fields are produced by the motion of electrical charges commonly referred to as current, and are measured in units known as milligauss(Mg). The electric and magnetic fields produced by 60 Hz electric power are referred to in this document as 60 Hz EMF.

At the present time it is difficult to say for sure if 60 Hz EMF is at all harmful to humans. Some epidemiologic studies suggest that 60 Hz EMF either causes health effects directly or promotes the development of health effects which were originally caused by some other adverse environmental or non-environmental factor. Other studies suggest no such relationship. With regard to cancer, even when an association has been demonstrated between some types of cancer and 60 Hz EMF exposure, it has not been shown that 60 Hz EMF was the definitive

cause of the cancer. Laboratory studies have demonstrated that biological changes within cell tissue cultures can be induced by 60 Hz fields, but these changes have not been linked to human health effects.

The scientific community's current understanding of 60 Hz EMF exposure and its possible relationship to health has focused on several different diseases. Although conclusions regarding the amount of risk vary, most research indicates that children exposed to somewhat higher levels of 60 Hz EMF in their home environment have at least a one and one half to two times greater chance of being diagnosed with leukemia and cancers of the brain and nervous system than children exposed long-term to 60 Hz EMF at lower levels (London, 1991) (Savitz, et al., 1990).

In adults, a smaller but increased risk of leukemia and cancers of the brain and central nervous system has been shown among workers in the electric power generating and electronics manufacturing industries, occupations which are likely to have higher 60 Hz EMF exposure (Folderus, 1992). Only a slight increased cancer risk has been observed among adults exposed to elevated field strengths of 60 Hz EMF in residential settings.

Genetic Predisposition

Familial aggregation of leukemia -- a phenomenon which could result from inheritance or from a shared environment -- is known [Linet, 1985; Heath, 1982; Sandler and Collman, 1987] -- usually with a single cell type occurring in all affected family members. Investigators have generally failed, however, to find blood-cell or other markers that typify affected members of leukemia-prone families [Linet, 1985]. Heath [1982] reports that numerous surveys have considered the question of familiarity without consistent evidence of more than faintly increased risk to close relatives of leukemics. This author maintains that familial aggregation, if it does

exist, seems to involve mainly CLL, which does not occur in childhood. Few researchers have attempted to describe variation in leukemia incidence or mortality with socioeconomic status, and results have been equivocal -- with some studies failing to find any differences, some showing a positive relationship, and some suggesting a negative association at least with some subtypes [Linet, 1985]. The hypothesis has existed for some time, however, that the increases noted above in worldwide incidence and mortality and other within-country trends are related to improved living conditions -- an association which may be confounded by industrialization or urbanization.

Parental Occupation

Considerable attention has also been given to the possible relationship between childhood leukemia occurrence and parental occupational exposures. Although a better case could perhaps be made for a link between maternal exposures (especially during pregnancy) and childhood cancer, most studies of this subject have concerned paternal exposures -- probably because of the historical predominance of men in the work force, and particularly in those jobs in which chemical exposure would be likely. Savitz and Chen [1990] have noted that, for father's occupation to be causally linked to childhood cancer, either the child would have to be exposed directly to chemicals brought into the home, or the chemicals would have to alter the father's germ cells.

In 1990, Savitz and Chen found 24 relevant studies to review. All had case-control designs, and most relied on job titles recorded on birth certificates or reported at interview for exposure assessment. Many job titles were found to be associated with childhood cancer occurrence, but there were inconsistencies in the data, which Savitz and Chen thought might have derived from inconsistency of design (e.g., some studies concentrated on particular cancer

types, subtypes, or age groups, while others considered childhood cancer or childhood leukemia in the aggregate).

The reviewers seemed to be of the opinion that, because of weaknesses in the study designs, particularly with respect to exposure assessment, the research thus far completed was useful mainly as a screening mechanism and that in future studies further attention should be paid to paternal paint exposure and paternal hydrocarbon exposure because of the relatively strong and reproducible associations found between jobs that would afford these exposures and childhood leukemia.

Radiation

Leukemia as a late effect of radiation exposure has been recognized since 1944 (a decade after Marie Curie's death from radiation-induced leukemia [Lancet editors, 1984]), when March reported that this disease was nine times more commonly recorded as a cause of death among radiologists versus other physicians [Linos et al., 1980; Gee, 1987; Linet, 1985; Berry, 1987]. Today, cancer is well recognized as the principal health hazard associated with exposure to small doses of ionizing radiation [Fry, 1981; Rossi, 1980; Rahn et al. 1984; Upton, 1982; Gofman, 1979], most of our understanding of the carcinogenic effects having been gleaned from studies of survivors of the atomic-bomb detonations that ended World War II.

The low leukemia death rates found among those in utero ATB (20 cancer deaths per million per rad [Mole, 1975]) can be contrasted with the elevated leukemia rates (240 per million per rad [Mole, 1975]) associated with prenatal X-ray exposure in the Oxford Survey of Childhood Cancers (OSCC) [Knox et al. 1987] -- a finding which was at first rejected because of its disagreement with the A-bomb data as well as certain design issues which were resolved in more recently conducted studies of the same phenomenon [Doll, 1989]. Interesting in this

regard are cytogenetic data which have suggested that X-rays may be three times as effective as gamma rays at causing certain chromosomal aberrations at low doses [NCRP No. 64, 1980].

METHODS

This report presents the findings of the expanded case-control study of leukemia among Woburn children. An appendix to the report (Appendix I) provides a discussion of the epidemiology of leukemia, including information on known risk factors for leukemia, as recorded in the scientific literature. The report has been peer reviewed by a panel of experts outside of the DPH. Their comments can be found in Appendix II.

The specific goal of the study was to determine whether childhood leukemia was associated with exposure to water from Wells G & H. Other risk factors for leukemia have been evaluated and the results of these analyses are also presented.

Study Design

The Woburn Childhood Leukemia Follow-Up Study is a matched case-control study. A case-control study is a specific research design best suited for use in circumstances in which individuals have been identified with a particular condition or disease (the childhood leukemia cases) and researchers are interested in determining past attributes or exposures these individuals may have had which may have been relevant to the development of the disease. Controls in this study are a group of individuals in whom the disease of interest is absent but who represent those persons who might have become cases as they are drawn from the same population. They are selected for comparison based on specific matching criteria.

Matching refers to the pairing of one or more controls to each case on the basis of their similarity with respect to selected variables that can potentially confound or bias the results.

Characteristics of individuals such as date of birth, race, or sex can be used as a basis for matching. If cases and controls are matched on specific characteristics, any differences between them would then be attributable to some other factor. Matching therefore is a method that allows for more efficient control of confounding in the analyses by assuring a more even balance of subjects within strata of the matched factors than would be obtained through use of an unmatched sample. Concern that certain attributes of the study subjects are interfering with the researcher's ability to identify a true association between the disease in question and a potential cause are lessened. Past information regarding the cases and their matched controls was collected at interview for time periods corresponding to the preconception, gestation, and childhood of study subjects up to the date of diagnosis of the matched case.

Case Definition

A case is defined as a child who 1) was diagnosed with leukemia prior to their 19th birthday 2) was diagnosed between January 1, 1969 and August 31, 1989 and 3) was a resident of Woburn at the time of their diagnosis.

Childhood leukemia cases were chosen to be no more than 18 years of age to maintain consistency with the methods of the original MDPH study (Cutler, 1986). Cases diagnosed prior to 1982 were identified from medical records in one of the four medical centers that diagnose and treat children with leukemia in the Boston area. Cases diagnosed since 1982 were identified from the Massachusetts Cancer Registry. The International Classification of Diseases for Oncology (ICD-O, 1976) system was used to define leukemia in accordance with the National Cancer Institute's guidelines (Appendix III). Twenty-one subjects fit the case definition and were included in this study.

Confidentiality

At the time of study subject selection, identifying information was abstracted from school records to assist the project director in locating parents of the study subject. The information was maintained on files at MDPH and was available only to researchers involved in this study.

The initial contact letter sent to all study subjects explained 1) the general purpose of the study, 2) a brief outline of the information that would be requested at the time of the interview, 3) the right of the study subject to withdraw from the interview at any time, and 4) that confidentiality of all collected information will be maintained by MDPH. All subjects who agreed to participate in the study were asked to sign a consent form that reiterated what was stated in the letter (Appendix VIII).

Only personnel working on the project had access to completed interview forms and computer files. All data was stored in an encrypted format, limiting its access to authorized researchers.

Confidential information collected for the purpose of this study is protected under Massachusetts General Laws pursuant to the provisions of General Law chapter 111, section 24A. This law provides that the Commissioner of the Department of Public Health may authorize or cause to be made scientific studies and research that have for their purpose the reduction of morbidity and mortality within the Commonwealth of Massachusetts. All information, records, reports and data received by the researcher in connection with studies and research authorized under section 24A must be kept confidential and may be used solely for the purpose of medical and scientific research.

Etiologic Period

The etiologic period for this study is defined as the period of time for which study subjects and subject parents could have received exposures that may have contributed to the case's leukemia diagnosis. Analyses in this report will address the etiologic period in its entirety or by time frame subsets that compose the period of etiology.

Control Definition and Ascertainment

In the 1981 study, two controls were selected for each case. The controls were matched to the date of birth (± 2 years), race, and sex of a case. Area of residence within Woburn was also used as a criterion for control selection in the 1981 study. One of the two controls was selected so that the child's residence was in that section of Woburn most distant to the residence of the leukemia case. The second control was selected so that the child lived either on the same street or the street adjacent to the case.

The cases diagnosed since the completion of the 1981 study have demonstrated a more random distribution of residences at diagnosis than the original case group. It was therefore decided to randomly select controls from among Woburn residents for this analysis. Two controls were selected for each of the 21 cases matched on race, sex, and date of birth ± 3. Controls must have been Woburn residents at the time of the diagnosis of the matched case.

The cases were matched to controls by date of birth to assure that cases could be compared to controls who were potentially consuming Woburn public water during the same period of childhood development and during the same period of the wells' history of operation. Differences in potential exposure among matched subjects would therefore reflect differences in residential well water distribution patterns, not differences in concentrations of potential contaminants in Wells G and H over time.

The Superintendent of Schools in Woburn allowed MDPH access to public school records for use as a database in the selection of potential controls. Cases old enough to attend school attended Woburn public schools. Controls were selected from school rosters of public school classes that met the control selection criteria. Information regarding the selected controls was abstracted from school records and MDPH research procedures protecting confidentiality were followed as previously discussed in the confidentiality section of this document.

The City of Woburn has one public high school but several elementary and two junior high schools. For cases whose controls were high school aged or older, controls were selected from permanent record cards kept at the Woburn High School. The high school card files were kept in alphabetical order by year of graduation. The set of cards for each year of graduation represented all children who entered Woburn High School as freshmen for that graduating class. If class members dropped out of school, or left Woburn High School prior to graduation, their cards were kept in the file and thus were still available as potential controls. Children who may have left the Woburn school system while in elementary or junior high school would not be represented in this file as their records would have remained at the last public school they attended.

Woburn elementary and junior high school students could have been in attendance at several possible schools throughout Woburn. Their records were thus not immediately accessible in one central file. Matching for these children was completed by obtaining computer generated alphabetical listings of the children from all primary schools by year of graduation. This allowed for the same geographically independent matching scheme used for high school children to be used for matching younger children in the neighborhood-specific schools. All

cases were or would have been at least primary school age at the time of control ascertainment, therefore school records were the only data source necessary for the obtainment of controls.

Once the correct roster was obtained, controls were selected from school department records as follows. A numerical identifier was assigned to each class member sequentially from 1 to N, N being the total number of children in the class. A three digit random number was generated from a table of random numbers and the child who corresponded to the random number was identified. The child's records were examined to determine if the child matched the case based on the sex and age criteria. If the child did not match, or the random number generated was greater than the number of students in the class, a new random number was selected and the procedure was repeated.

For persons currently attending or having finished high school, if the initial matching criteria discussed above were met, the high school permanent record card was examined to determine if the potential control was in the Woburn school system on the date the case was diagnosed. This information was not always available on the card but often dates of transfer from other school systems were indicated. If the child was in the Woburn school system on the case diagnosis date, the control was selected as a possible match pending later verification of residence at the time of case diagnosis. If the child transferred into the Woburn school system after the date of diagnosis, it was assumed that the person did not live in Woburn on that date, therefore the potential control was eliminated, and a new control selected.

For elementary or junior high school students, if the random number selected resulted in a match based on the above discussed age and sex criteria, no further verification of residence could take place at that point. Information available on the computer-generated roster contained

only the current residential information of the students. The control was then selected pending later verification of residence at the time of case diagnosis.

Four potential controls were selected for each case to allow for replacement of controls whose families (1) did not reside in Woburn at case diagnosis, (2) might refuse to be interviewed, or (3) might be unavailable for interview. No controls were considered as final control selections until Woburn addresses were historically confirmed by the use of Woburn city directories.

Woburn city directories corresponding to the year the case was diagnosed were consulted to determine if each selected control or control's immediate family was listed as a resident of Woburn in the year of case diagnosis. If so, the potential control was considered valid and contact for interview was attempted. If the control or control's family was not listed, city directories for two years prior to the case diagnosis date were examined in the event the potential control's family was omitted in error from the directory for the year of diagnosis. If the potential control was found in the earlier directories it was considered a valid case. If the control was not found in any of these directories, it was excluded as a possible control. If there was no directory available for a necessary year, the control was not eliminated. Instead, residence at date of the case's diagnosis was confirmed when the control's family was contacted. Once a control was considered as valid the current city directory was used to confirm the current family residence and an attempt to contact the control family was made.

When parents of potential controls were contacted, they were asked whether the potential control was a resident of Woburn on the date of diagnosis of the matched case. If so, the residence criteria were met, and researchers attempted to schedule a time for parents to be interviewed.

Confirmation of a match with regard to race was not accomplished until the time of the interview. If it had been learned during the interview that the race of the case did not match that of the control, the interview would have been completed but the control would later be replaced.

Search Procedures

Search procedures were employed to locate the current address of cases and controls and/or their parent(s). Woburn has a fairly stable population, therefore, it was expected that most subjects would still reside in the community.

The search procedure began with the information abstracted from the school record card. This data was current for school-aged controls and living cases as address information is constantly updated in school records. If a child moved out of town while still in school, the name and location of the new school was recorded by the school for the purpose of forwarding records and often a new home address was also available.

Several cases had died prior to entering school. Their death certificates provided their address at death and the names of relatives who could be contacted for current residence information. The Woburn city directory was a reliable resource in confirming or updating addresses. The directory's alphabetical listing of resident names provided a convenient method of identifying other relatives that could be contacted for updating or verifying an address.

The MDPH has access to the Department of Motor Vehicles computer database. If local records provided no new information regarding the location of study subject families, drivers' license and automobile registration information files were searched. If the study subjects or their parents held a valid drivers license or registered a car in Massachusetts in recent years, their address at last renewal could be obtained.

If school records, telephone directories, city directories, motor vehicle records, and/or vital records information yielded no current information on control families, the control was replaced with the next matched control which had been chosen. Each of the 21 case families was located using the above mentioned data sources.

When the current address of a subject's family was identified, a letter was mailed addressed to the subject's parents explaining the purpose of the investigation. For case families, two different letters were prepared. Those families who participated in the original 1981 study (Appendix IV) were thanked for their previous participation and then asked to participate in the new research. The case families of children who were diagnosed after the completion of the first MDPH were sent a letter requesting their participation (Appendix V) which explained the purpose of the investigation in more detail than that sent to the case families who participated in 1981.

Control families received a similar letter (Appendix VI) which explained the elevated rates of childhood leukemia in Woburn. It identified the member of the family chosen as a control and briefly described how that person was selected.

All letters described the voluntary nature of the research and its confidentiality as previously described in the confidentiality section of this report. They explained that interviews would be conducted in person and that an interviewer would contact study subject families within ten days to invite their participation and arrange a convenient time for interview. If it was learned during the search that parents of study subjects no longer shared the same residence, each parent received a separate copy of the letter and they were each asked to be interviewed individually.

Within ten days the interviewer attempted to contact the subject families by telephone. If the phone number was unlisted, a letter (Appendix VII) was sent asking the family to contact the Bureau office so an appointment could be arranged. If those persons with unlisted numbers did not call the office within ten days, the interviewer visited the home in an attempt to obtain a response. When the interviewer contacted the potential subject parents, the interviewer answered any questions the participants might have had regarding the study and attempted to schedule an appointment for the interview.

For controls, refusals were replaced with the next best match from the subject pool and the procedure was repeated. Case families could obviously not be replaced and were therefore lost from the study sample. If controls agreed to participate, the interviewer then questioned the parents to confirm their eligibility regarding residence. As previously mentioned, school and vital records could not always confirm that the control resided in Woburn at the time of the case diagnosis. This was most often true if the case was diagnosed as a preschooler. Controls had to have been Woburn residents before they attended school to be considered a match and their school records would not indicate the family address before enrollment. Controls whose families did not live in Woburn at the time of case diagnosis were replaced.

Data Collection

All interviews, both cases and controls, were conducted by the same interviewer; therefore bias resulting from interviewer variability was eliminated. Interviews were conducted in person unless extenuating circumstances made in-person data collection impossible (two fathers were interviewed by telephone). Most persons preferred to be interviewed at home. If both parents resided at the same address at the time of the interview, the interview was scheduled so that both parents could be present (Table 3). If study subjects resided in the home,

they were asked not to participate in the interview or assist the parents in responding to specific questions. This assured that the quality of responses would always be dependent on the quality of the recall of the parents and not influenced by the availability of the study subject for interview.

Upon arrival at the study subject family's home, the interviewer asked the parents to read and sign a consent form stating that they agreed to be interviewed (Appendix VIII) and then read and consider signing a consent form explaining Massachusetts laws which protect confidential information collected by MDPH. The consent forms would allow MDPH the authorization to review the medical records of the study subject if necessary for the purposes of completion of this investigation (Appendix IX). In order to proceed with the interview, it was necessary for parents to sign the consent form agreeing to be interviewed but the parents could choose not to sign the consent form allowing medical record access if they so chose.

The interview form was divided into two questionnaires, a mother's questionnaire and a father's questionnaire (Appendix X). The mother's questionnaire was designed to gather information regarding demographics, residential information for the mother and child, occupational history of the mother, maternal medical and reproductive history, medical information regarding the child, and life-style questions concerning the mother and child. The father's questionnaire contained questions concerning his military and occupational history. The questionnaire also contained questions identical to the mother's questionnaire regarding mother and child's occupational history, child's medical history and life-style habits.

If both parents were present at interview, the maternal questionnaire was administered to both parents in its entirety. The first part of the father's questionnaire containing father's

occupational information was also administered and the interview was ended after completion of the paternal occupational exposure section.

Mothers responding alone would be asked all the questions contained in the mothers' questionnaire and those questions in the fathers' questionnaire which were not redundant to the mothers'. If the father was interviewed separately, he was asked to respond to his questionnaire which included questions specific to his military and occupational history, the child's residential history and certain questions concerning the child's medical history. If the father was interviewed but the mother was not available for interview, the father was asked to respond to all questions on both questionnaires. If a parent was deceased or unavailable for interview, the participating parent completed the maternal and paternal information in both questionnaires to the best of their ability.

Duplicate questions were asked of fathers when parents were interviewed seperately, in order to validate or complete missing information from one or the other parent. Mothers' responses were always the responses of choice for maternal occupation, maternal and child medical information and life style questions, when available. Fathers' responses were always the responses of choice for issues regarding fathers' military history, occupations and occupational exposures. Conflicting responses with regard to residential history required the interviewer to re-contact each parent by telephone for further verification.

Due to the age differences among cases, certain levels of recall bias are unavoidable. Study subjects vary in age up to thirty years. This means that when parents respond to questions, certain parents are being asked to recall events that may have occurred up to thirty years earlier, while other parents are recalling events occurring only a few years past.

The questionnaire was promptly edited after the in-person interview was completed. Responses were thoroughly examined for clarity and consistency. It was particularly important that residential information was complete with respect to street address and that dates of residence were consecutive with no gaps in time. These parameters would later be essential in the exposure assessment, as the Wells G and H water distribution model was strongly dependent on the dates of residence for each study subject.

Occupational history information and other chronologically dependent data such as years of attendance in specific schools were also verified in this manner. Inconsistencies could be identified if activity dates did not coincide with life events, such as the changing of a town of residence without moving from one school to another.

Exposure Assessment

General Approach

The primary exposure of concern for this investigation is the potential consumption of contaminated water from Wells G and H by Woburn residents. Researchers in the initial DPH investigation had no information regarding the distribution of the water from the wells throughout Woburn's neighborhoods.

The subsequent Harvard study, completed in 1982, utilized a draft report by the Massachusetts Department of Environmental Quality Engineering (now the Department of Environmental Protection (DEP)) that estimated regional and temporal distribution of water from Wells G and H between October 1964 and May 1979, the period of the wells' operation (Waldorf and Cleary, 1983). The DEP study presented a model of the Woburn water distribution system and divided the city into five zones of graduated exposure to Wells G and H.

The DEP water distribution model estimated on a monthly basis which residential zones received none, some, or all of their water from Wells G and H. Exposure scores for each study subject were calculated, representing the amount of water from Wells G and H the subject's household was likely to receive. Information was collected on the residential history of each family member.

For the follow-up study and the Woburn Environment and Birth Study (WEBS), the DPH sought to refine the DEP water distribution model as much as possible. DPH contracted Peter Murphy, Ph.D., a Hydraulic Engineer to refine the original work done by DEP. Dr. Murphy then refined the original model by considering more detailed information concerning the water to a level much more precise in geographic and quantitative distribution than the original five-zone model (Appendix XI).

Development of Water Distribution Model for Wells G and H

The Woburn water distribution model estimated the relative proportion of water from Wells G and H that reached various Woburn neighborhoods. Full documentation of this model is located in Appendix XI. The model had two fundamental components: input data describing the Woburn water system under two historical sets of conditions, and a computer program for determining the flow of water through the pipe network to the users. The model was calibrated using pressure test data collected at five fire hydrants and by comparing reservoir flows and adjusting for assumptions for pipe roughness. Validation was accomplished through field tests using a fluoride tracer. A numerical monthly exposure index was developed that reflected the proportion of contaminated water that reached each hydraulically distinct neighborhood for each month that Wells G and/or H were pumping. Assignment of street addresses to each

hydraulically distinct neighborhood allowed for the calculation of cumulative exposure for individual births. Sources of error for the various components of the model were estimated. An independent scientific peer review of the model was conducted. As a result of this, additional analyses were performed to assess the degree of variation in the reported spatial and temporal spread of the contaminated water, and to assess the sensitivity of the exposure index to the internal roughness of the pipe network.

Until May 1979 when Wells G and H were closed, the Woburn water supply system relied exclusively on groundwater pumped by a number of city wells into the pipe distribution network to both residential and commercial consumers. The distribution system was regulated by pump control valves and water storage tanks and reservoirs.

The first component of the water distribution model required a number of specific types of information about the pipe network. This included all of the principal water pipes, their ages, types, i.e., asbestos, cement or cast iron, dimensions, locations and interconnections.

Information regarding leakage flow was an important addition to the model by Murphy because significant leaks would increase demand that would not be accounted for by residential and commercial use. It was assumed that leakage flow was uniformly distributed throughout the system. Because Woburn did not have water meters that quantified residential use, average residential water consumption was estimated by applying the value of 370 gallons per day to each residential address. Meter readings from commercial users for 1984 indicated that they used approximately 21% of the total water.

The water bills of 1984 were used to generate address lists for residential consumers. The amount of residential and commercial usage, coupled with street address and knowledge of the layout of the pipe network, allowed for the identification of fifty hydraulically distinct user

demand areas within Woburn. Boundaries for the user demand areas (nodes) were placed in the middle of the pipe connecting the two neighboring nodes.

In addition to the pipe network and consumers, there were also reservoirs and pumps that were influenced by demand within the distribution system. All well pumps were metered so that data was available to document the daily pumping history. Both the volume of water pumped and the number of hours during each month that pumping occurred were obtained for all combinations of the contaminated wells. Monthly records of the average flow rate for the uncontaminated city wells were also obtained. Thus, the average monthly percentage of the municipal drinking water supply that came from Wells G and H was able to be determined.

The computer analysis of water distribution utilized the basic principles of conservation of mass and energy to water flowing through the system. The mass conservation principle was applied by assuming that the pipes did not leak, and that the consumers took water out of the system only at the pipe junctions. It was also assumed that water entered the system at the nodes corresponding to the wells and reservoirs. Thus, the net flow rate into each user demand node was assumed to have equaled the user demand of that pipe junction.

The energy conservation principle was expressed in terms of height or "head". The total head was comprised of three different kinds of energy: potential energy, i.e., the elevation of the centerline of the pipe above sea level; kinetic energy per unit weight, i.e., the square of the flow velocity divided by twice the acceleration of gravity; pressure energy per unit weight, i.e., the pressure divided by the specific weight of the water. The energy lost to friction as the water flows through the network was determined by relating the loss to the flow rate through the pipe, the length and diameter of the pipe and the roughness of the inner wall of the pipe.

The computer used a large number of linear and non-linear equations that were organized and solved to determine the flow rates through each pipe and the total head at each pipe junction. The input variables for the computer program were: pipe length; pipe diameter; pipe connections; pipe roughness; node water demand; node elevation; reservoir level; pump flow rate; pump total head; well water level; check valve sites; and pollutant concentration.

A mixing program was added to the model to analyze pollutant movement and mixing within the system by applying the principle of mass conservation to the mass of pollutant in the water system. The assumptions were: the pipe's flow rates were not changed by the addition of small amount of dissolved contaminants to the water; pollutants moved through the pipes with the water without changing concentrations; the inflows mixed completely at each pipe junction; consumers got the mixed water of that node; and outflow pipes from each pipe junction carried the mixed water to the farthest point of the pipe network.

Model Calibration and Validation

A calibration process was performed in 1984 using 1983 insurance company pressure test data from fire hydrants. The insurance company conducted the tests under two sets of conditions: normal demand and demand produced when individual fire hydrants were opened and their outflows were added to the normal demand. The calibration process compared the 1984 model with total head values generated from the 1983 pressure tests and other data for the water system on the days of the hydrant tests. This initial model was used to calculate the flow patterns and the total head distribution of the system.

The calibration data for conditions of demand with individual fire hydrants open was compared with data produced by the model, and roughness values of the pipes between the individual hydrants and their water sources changed to reduce the difference between the data

and the model. The error level of the calibration process, after all adjustments had been made, was 0.9 feet total head. Root mean square head difference was 6.2 feet.

Validation studies were carried out using fluoride as a tracer within the water system to see how closely the model could predict concentrations of fluoride in the water. A filed test was done in 1985 in Woburn. After Wells G and H were closed in 1979, the Metropolitan District Commission (MDC) provided a supplementary water supply. This water was fluoridated at the level of 1.07 ppm, while the rest of Woburn's supply contained fluoride at the 0.07 ppm level. The qualitative information predicted that the MDC water would be distributed primarily in East Woburn, the southwest would receive water mainly from other non-contaminated Woburn wells, and the northwest area of the city would receive a mix of water. Field tests indicated that there was approximately a one node difference between the expected and actual boundaries of fluoridated and unfluoridated water. Overall, 72 percent of the field test predictions were within 0.2 ppm of the observed values.

Field validation indicated that the ability of the model to predict the boundaries of the area receiving Wells G and H water was accurate to within one node, and was able to predict mixture concentrations with an average error within 10 percent of the maximum concentration, and a root mean square error within 30 percent of that level. While large errors in the mixture concentrations were possible along the boundaries, nearly 70 percent of the predictions were within 20 percent of the measurements.

Scientific Peer Review

The Peer Review Committee for the Woburn Water Distribution Model was comprised of four senior scientists with expertise in the fields of engineering and modeling, mathematical modeling, sanitary engineering and epidemiology, and environmental statistics and public health.

All had previous experience in the development, application or use of these types of models in assessing exposure to the public from chemical and/or microbiological contaminants in water distribution systems. The Committee was chaired by Shanna Swan, Ph.D., from the California Department of Health Services. The Committee was given the following charge:

- The primary charge was to evaluate whether the model and its application to the Woburn water supply system resulted in accurate exposure predictions for each user demand area for each month. To accomplish this the Committee was asked to: examine the overall strengths and weaknesses of the model and contrast it with any other options; examine how the model was applied to the Woburn water distribution system, specifically the input data and assumptions, and the calibration exercises; examine the level of validation of the model including the mixing term for all time periods analyzed; examine the sources of error, its quantification and how this would affect the exposure index; examine the methods of deriving the exposure index. The Committee was asked to fully discuss the above topics and generate a simple list of conclusions and suggestions and/or recommendations.
- A secondary charge was to discuss and make suggestions regarding the use of the model in the data analysis, i.e., relative benefits of assigning exposure by use of cumulative exposure index; analysis of exposure as a categorical and/or continuous variable; and selection of time periods and outcomes for analysis.

The Chair wrote findings and recommendations based on oral and written comments from the members. The Committee's overall conclusion was that additional work was not essential for creating exposure indices for use in epidemiologic studies. The Committee commented that the work reflected: thorough attention to detail in handling all data; use of good

engineering judgment and common sense in making assumptions and adopting approaches in areas of uncertainty (e.g., no metered information on residential water use); unbiased interpretation of data and results; and candor in reflecting the magnitude of uncertainty and probable error in assumptions, parameters and conclusions. A few refinements were suggested that might further increase confidence in the model. Dr. Murphy incorporated the suggestions into the final model.

Water Exposure Index

The water distribution models were used to generate typical water distribution patterns for each month when either or both of the contaminated Woburn wells were pumping. The mixing program was then applied to calculate the fraction of drinking water supplied to each user demand area that came from Wells G and/or H. The analysis for each month included periods with wells on and off, as well as the maximum, minimum and average peaking factors that described the demand conditions of the daily Woburn water-use cycle. The monthly analysis, therefore, took into account each of these conditions in performing the water distribution calculations and the mixing program.

The exposure index was defined as the product of the fractions of the time during a month when any water from Wells G and H reached the user area and the fraction of the water supplied to that user area that came from the contaminated wells. The unit for the exposure index was months.

The assignment of exposure to each etiologic period was the product of a three-step process (for simplicity, the term "node" will be used throughout the following discussion to refer to "user demand area"):

1. assigning each segment of the etiologic time period to a node on the basis of street address,
2. linking each time period with node-specific cumulative monthly exposure values, and
3. calculating cumulative exposure for each time period specific to its assigned node and dates of occurrence.

For each member of the study population, seven cumulative exposure scores were calculated: one for the entire etiologic period, the pre-conception period, each trimester, the pregnancy overall, and the period of time between birth and case diagnosis. Each calculated exposure score for each member of the study population was merged with the other data collected during the interview for use in statistical analyses.

Two types of exposure index values were calculated for each user demand area for each month. The first type was a monthly exposure score reflecting the proportion of water from Wells G and H supplied to each user demand area by month, ranging in value from zero to one.

For example, a value of 0.75 for a specific month indicated that 75% of the water supplied to a given user demand area for that month was from Wells G and H (the remaining 25% was supplied by the other wells in the Woburn water supply network).

The monthly exposure index value for each user demand area used in the calculation of the exposure index values for each individual study subject. The residential data for each subject family was linked to exposure as estimated by the water model by linking the address to its corresponding user demand area and the dates of residence at that address to the exposure index values for that time frame. The cumulative exposure index for a study subject or the subject's mother 2 years before and during pregnancy was derived by summing the monthly exposure

indexes for all months of residence in a specific user demand area. If subjects moved within Woburn during the etiologic period their cumulative exposure at each address was calculated in the same way and the total values in each address were summed to generate a study subject-specific exposure index.

Due to fluctuations in the proportion of Wells G and H water supplied to any given node in any given month, the exposure level was calculated for each time segment in order to provide measures of exposure for discrete periods within a time segment as well as for the etiologic period as a whole. This was done by isolating the exact months of the beginning and end of a time segment and determining the corresponding cumulative monthly exposure values for those months in the time segment's assigned node. The cumulative exposure value corresponding to the beginning data of the time segment was subtracted from the cumulative exposure value corresponding to the end date to yield an exposure calculation after the duration of the time period of concern. For example, a pregnancy assigned to Node 43 had a beginning date of January 1, 1976 and end date of October 1, 1976. The cumulative amount of Wells G and H water delivered to Node 43 just prior to January 1976 was 63.64 months of water. By the end of September 1976, Node 43 had received 70.83 months of Wells G and H water. Thus, in the nine-month interval of the pregnancy, the fetus potentially had been exposed to 70.83 - 63.64 = 7.19 months of Wells G and H water. The same arithmetic process was duplicated for each time segment and the etiologic period overall.

The beginning date of pregnancy was taken to be the date of a mother's last menstrual period (LMP) and the end of pregnancy was taken to be the date of birth (DOB). Trimesters were defined in 15-week intervals beginning with the date of LMP. The third trimester began on the date 28 weeks after LMP and ended on the DOB.

The beginning and end dates of most pregnancies did not coincide with the first or last day of a month. Therefore, when a pregnancy portion began or ended sometime during a month, the exposure value for that month was based on the number of days during the month that the pregnancy actually occurred. For example, consider a pregnancy assigned to Node 43 and with a DOB of September 10, 1976. For Node 43, the cumulative monthly exposure value in September 1976 was 70.83 and the previous month's value was 69.93. The difference between these two exposure values corresponds to the individual monthly exposure value for September alone (i.e., 70.83 - 69.93 = 0.90). Since the birth occurred on the 10th of September, the actual exposure in September would be computed as: (10 days/30 days) *0.90 = 0.30. This computed value for the final partial month of pregnancy would be added to the previous full months cumulative exposure value to arrive at the adjusted final cumulative exposure value for the end date of pregnancy (i.e., 69.93 + 0.30 = 70.23).

As discussed above, a complete residential history was obtained for each study participant. This allowed for the linking of study subject residential data to monthly exposure data from each node within Woburn. At the interview the source of water for the homes were confirmed. All study subject houses used public water to supply their homes during the etiologic period. None used private wells as a water source. Cumulative exposure values for each study subject were generated by summing monthly exposure values for each residence two years prior to conception to the date of case diagnosis. Cumulative values were also generated for more specific time periods throughout the etiologic period. These time periods were: 2 years prior to conception to date of conception (based upon gestational age of the child as reported by the mother), first trimester, second trimester, third trimester, and the period between birth and date of diagnosis of the case.

Residential information for each case was comparable by study design to that of its two matched controls. This means that each matched triplet (the case and its two controls) had Wells G and H water exposure values based on the same length of residence in Woburn. By definition, all study subjects had the same length of exposure 2 years prior to conception and the same first and second trimester length. The length of the third trimester varied depending on the length of gestation of each study subject. The length of the exposure which occurred after the birth of the study subject depended upon the age of the case at diagnosis.

Cumulative exposure data were assessed based on exposure scores generated by two methods. Data specific to each month of residence was summed based upon the location of residence. Secondly, water exposure data was averaged over time to address differences in the patterns of exposure that might not be represented using cumulative values. For example, if a study subject had relatively little exposure for most of the time period of concern but had particularly high exposure for a short time, this subject might have the same cumulative exposure as someone who had a fairly steady exposure for many years. Cumulative exposure metrics would be the same for those persons, average exposure metrics would not. Average and cumulative exposure metrics were assessed as independent variables and then entered as components of multivariate analyses. Virtually no differences were seen between cumulative and average exposure results. Cumulative exposure data will be presented in the results and used in the discussion sections of this report.

In an attempt to most clearly address potential dose-response relationships between the exposure and outcome variables, the exposure values were parameterized in several different ways. Trichotomous parameters based on the distributions of the controls as well as simple

dichotomous parameters which reflect an "ever versus never" exposure relationship were examined.

Other Exposures

60 Hz EMF Exposure

In the United States, electricity is supplied by power lines to homes, offices, and factories at a frequency of 60 cycles per second or 60 Hertz (Hz). Electric and magnetic fields that result from 60 Hz electricity are known as 60 Hz EMF. As discussed in the literature review, concerns regarding 60 Hz EMF have been raised by researchers whose work suggested a possible link between the risk of certain cancers including leukemia and exposure to high tension power lines and neighborhood distribution lines. As part of this investigation, researchers attempted to assess 60 Hz EMF exposures for cases and controls.

The researchers' original intent was to conduct magnetic field measurements within each home as well as utilize wire coding methodology to assess potential correlation between wire configurations, magnetic field measurements and their relationship to childhood leukemia. Technical restraints forced the restriction of the scope of the 60 Hz EMF portion of the study protocol to the assessment of distribution line wire code configurations.

Efforts were thus focused on the application of the Wertheimer-Leeper wire coding method to study subject residences. Wire coding requires examination of electrical distribution lines outside the home and does not require access to residential property. It is also likely that wire configuration is a stable indicator of electric and magnetic field levels over time. Power distribution lines in communities with a predominance of older neighborhoods such as Woburn

are unlikely to change significantly over time, as space for intra-neighborhood expansion is limited.

Of the 21 original case families, 19 chose to participate in this study. Cases were each matched with two controls. For one participating case, a control proved ineligible after analysis began resulting in 37 matched controls rather than the intended 38. There were therefore 56 total study subjects.

Examination of the residential data obtained from the study questionnaire revealed that the 56 study subjects occupied 91 different residences within the etiologic period. Of these 91 residences, six were located in communities other than Woburn. It was decided the researchers would not code residences in other communities as some were a significant distance from the study area.

A data collection form was prepared which provided a check list of parameters to be examined at each residence. A research assistant from MDPH was trained according to the Wertheimer-Leeper method (Chartier, 1988) used in Kaune's research (Kaune, 1994). The research assistant was instructed regarding the wire configuration characteristics significant to the Wertheimer-Leeper model. A code number was assigned to each study subject address to assure that the field technician was blinded regarding whether a case or control occupied a particular residence. Each residence of interest was examined, wiring patterns were sketched onto a coding form and later scored using an algorithm devised by Kaune et al. (1990) (Appendix XII).

The Wertheimer-Leeper coding scheme is based on the premise that wiring configurations for residences fall into four categories each representing a different level of potential electromagnetic exposure. These are identified as very high current configuration

(VHCC), ordinary high current configuration (OHCC), ordinary low current configuration (OLCC), and very low current configuration (VLCC).

Wertheimer and Leeper assign a current configuration based on three parameters, the size of the wires nearest the residence, the distance the wires are from the residence, and the distance the transformer that supplies the house is from the residence. Their hypothesis states that those homes identified as VHCC are most likely to expose the residents to higher levels of electromagnetic radiation, OHCC to a lesser degree, OLCC still lower, and finally VLCC homes which expose residents to the lowest amount of 60 Hz EMF.

Occupational Exposures

Information concerning parental occupations was coded according to the system developed by the U.S. Department of Commerce for classifying individuals according to industry and occupation from information collected by the Census (Classified Index of Industries and Occupations, 1982).

Analyses include aposteriori assessment of occupations and industries examining the data specific to greatest frequency of industries and job types reported. This approach simply allows for the examination of relationships between most common industries and occupations reported and disease outcome.

A-priori assessment was also completed in which our occupational data was stratified by industries and occupations considered high risk (Savitz, 1990). Associations between these specific industry categories among parent and childhood leukemia among their offspring was assessed.

Occupation and industry categories with fewer than 10 total positive responses were dropped for analyses to assure statistical validity in interpretation of associations between the

industry or occupation and outcome. Relationships between occupation or industry and leukemia were examined as univariates and outcomes of significance were tested as multivariate analyses.

Interview items did not lead directly to an index of SES. Occupation variables were used to determine SES ranked by using the occupational components of the Hollingshead Two-Factor Index of Social Position (Hollingshead, 1958). The availability of extensive occupation information allowed for the ranking of occupations as a surrogate for socioeconomic status.

All study subjects were nineteen years of age or younger. The occupational index was calculated based upon the father's occupation if the father was living in the home and the mother's occupation if she was a single parent during the etiologic period.

Statistical Analyses

Methods

Statistical analyses included calculation of simple descriptive statistics, univariate and multivariate analyses designed to assess the relationship between exposure to Wells G and H, and other potential risk factors and their relationship to case-control status. Descriptive statistics and some univariate analyses were conducted using the ANALYSIS and STATCALC functions of Epi Info, version 5.01 epidemiologic software for microcomputers (Dean, 1990).

Conditional logistic regression for more detailed univariate and multivariate analyses was performed using SAS statistical software PHGLM procedure (SAS, 1988). A proportional hazards model was used to fit the conditional logistic regression to a case-control study design. Beta coefficients and standard errors were used for the determination of odds ratios as estimates

of relative risk and their confidence intervals. Correlation coefficients were generated using SAS statistical software CORR procedure (SAS, 1988).

Relative risks are statistics that are used to compare the risk of a given level of exposure to a referent category which is usually the lowest exposure level. Trends in the relative risks with increasing exposure were evaluated using chi square and SAS PHGLM procedures. The 0.05 probability level was used throughout the analysis in the construction of confidence intervals and statistical significance testing.

All data were collected in a dichotomous or categorically scaled format with the exception of the continuously scaled Wells G and H exposure data. Cumulative exposure and average exposure values for well exposure data were categorized for each study subject. Categorical boundaries were determined by listing all study subjects (cases and controls combined) in ascending order by exposure value. All subjects with zero exposure were considered to be the lowest exposure group.

The remaining subjects are divided into the upper two tertiles of exposure as follows:

1. If the total number of persons exposed is an odd number the subject who is the middle person in numerical position by ascending order of exposure is identified. This person is halfway between the person who has the lowest score among exposed and the person who has the highest score among exposed. This middle person is considered the least exposed person in the upper exposure tertile.
2. If the total number of persons exposed is an even number then the two persons representing the two middle positions are identified. The lowest exposed of the two becomes the highest exposed person in the middle exposure tertile.

3. If the middle identified persons share a common score with other study subjects or themselves, then a decision regarding their tertile is made which places all persons with same exposure value in the same tertile. They must be placed in the tertile that best balances the distribution of subjects among the tertiles with exposure.

Because of the small study population, it was anticipated that multivariate analyses would be limited by the small numbers. In order to assess the effects of a variety of different potential confounding variables, it is desirable to include many covariates in the statistical model at one time. Where the sample size is small, the inclusion of a large number of covariates limits the precision of the statistics resulting in odds ratios whose confidence intervals may be extremely wide.

In addition to applying standard multivariate methods in assessing the effects of several potential confounders, an attempt was made to increase the precision of the model while still considering the effects of several covariates simultaneously by using a method suggested by Tukey (1991). Tukey suggests creating a composite covariate that represents several different covariates and therefore reflects their overall effect on the outcome variable. The composite covariate is weighted based on the single term significance of each covariate of concern when run as an individual separate regression. The composite covariate is then entered in the model as a single term with resultant statistics reflecting narrower confidence intervals.

Continuos vs. Categorical Analyses

The majority of the analyses in this study were performed using regression analyses of categorical data. Although the Murphy water model generated discreet values representing estimates of exposure for each month of potential exposure to the contaminated wells, frequency

analyses of these estimates revealed a distribution of exposure values which were not truly continuous. Exposure scores were not evenly distributed along the range of possible values. As a result, categorical data analyses became the statistical method of choice.

Controlling for Confounding

Data pertaining to potential confounders was collected during the interview. Confounders, (factors related to both the disease under investigation and the exposure of interest) prevent proper estimation of effects and must be "controlled for" (i.e., held constant) through study design and/or analytic methods.

The current scientific understanding of potential causes of childhood leukemia is limited. Factors believed likely to confound results included demographic and lifestyle characteristics, medical history information, and environmental exposures other than from Wells G and H. Demographics and lifestyle characteristics included factors such as age of the child, sex of the child, race of the child, maternal age at birth of the child, socioeconomic status of the parents, maternal smoking during pregnancy, and maternal alcohol consumption during pregnancy. Medical history information included preexisting medical conditions of the mother and/or the child, x-ray exposure information, and medication use. Environmental exposures other than from Wells G and H include other household exposures such as to home chemicals, 60 Hz EMF exposure, and exposures which occur away from the home such as in school or while participating in activities away from the home. Work place exposures for parents are another important concern. Parents' job descriptions as well as consideration of specific types of work related exposures have shown to be important to consider as potential confounders.

The selection of matched controls based on the date of birth and sex of the child served to control for confounding effects of these variables during the design of the study. The

interview was designed to gather information relative to other potential confounding variables allowing for the control of their effects during data analysis.

Each variable was evaluated univariately to determine its possible contribution as a confounder. Variables for which positive responses occurred at a total frequency (cases and controls) of at least 10 and whose relationship with both leukemia and water exposure yielded an odds ratio greater than or equal to 1.5 were entered into the multivariable model. Variables were dropped from the multivariate analysis if they did not significantly affect the unadjusted odds ratio result. Four variables generally accepted in the scientific literature as potential confounders were extended into the model regardless of the statistical analyses described above. These four were 1) maternal smoking during pregnancy, 2) socioeconomic status, 3) maternal age, and 4) maternal alcohol consumption during pregnancy.

The approach to model building used involved the forcing in of potential confounders regardless of their effect on the relationship of primary interest or the fit of the model, log likelihood statistics were sometimes employed to evaluate the importance of interaction terms.

The parameter- (or coefficient-) estimation method employed by PROC PHGLM is conditional maximum likelihood estimation (CMLE). In general likelihood methods estimate the probability of the data observed under the model assumed. The values of the parameter estimates are those that maximize the likelihood function, and the associated p values give the probability that the null hypothesis (of no relationship) is true give the data. Matching (which "conditions" out nuisance parameters) necessitates the use of conditional methods, in which the matched sets are used as strata or blocks. CMLE involves calculating a portion of the likelihood function within each stratum.

RESULTS

Participation

Sixteen of the 21 childhood leukemia cases (76%) are male, five (24%) are female. Ten of the male cases and two of the female cases are deceased. Nineteen families (91%) agreed to be interviewed. In all but one instance the participating case families arranged for interviews to be conducted in their homes. The two case families who refused to participate were families of male cases who are now deceased. Both of these families participated in the original MDPH study.

In all but one instance, two controls were interviewed for each of the nineteen cases who agreed to participate. In that single instance it was learned after data collection had been completed that one of the two interviewed controls did not live in Woburn at the time of the case's diagnosis and was therefore ineligible. This control was excluded from the analysis leaving one remaining matched control for that case.

As Table 1 indicates, of the nineteen case families that were interviewed, for seven cases (37%) the originally selected control pairs were successfully interviewed. For the remaining cases, seven (37%) of the cases required one control replacement to complete the control pairs, three cases (15%) required two replacement controls to complete the control pairs and two cases (11%) required three control replacements.

Table 2 presents the distribution of control replacements by reason for replacement. Eleven control families refused to participate in the study and were subsequently replaced. Seven of these persons (64%) stated they were simply not interested in being a part of the study. Two persons (18%) stated that the questionnaire was an invasion of privacy, one (9%) family

felt that completing an interview about their child would provide no new information to benefit the study, and one (9%) family stated they were moving away and did not want to participate.

In seven instances, controls of choice were replaced when all methods of locating present residences of control families were exhausted. In six other instances, controls of choice were replaced with new controls when upon contact it was learned that controls were ineligible because they were not residents of Woburn for the entire time period between birth of the matching case and diagnosis. In one instance, the control was identified as ineligible because the family did not speak English adequately for completion of the questionnaire.

As described in the methods section, the first priority was to attempt interview study subject families at a time when it was convenient for both parents of the study subject to be present. As indicated in Table 3, we were successful in doing so for 13 (68%) of the case families and 31 (84%) of the controls. For two case families (11%) and two control families (5%) each parent of the study subject was interviewed at separate times, mothers completing the mother's questionnaire only, and fathers completing the father's questionnaire only. For four case families (21%) and four control families (11%) only one parent was available for interview. In these circumstances the participating parent completed both the mothers and fathers questionnaires. Parents who did not participate were either unavailable for interview or the participating parent requested that for personal reasons the second parent not be included as part of the study.

Description of Cases

Figure 1 demonstrates the distribution of leukemia cases in the study according to diagnosis year. As can be seen in the figure, the pattern of incidence between 1969 and 1975 was nearly identical to the pattern of incidence between 1977 and 1983 with the exception of the

occurrence of one additional case for a total of three cases in 1983 versus two cases in 1976. The pattern of incidence then changed with no cases diagnosed after 1986.

Table 4 illustrates the distribution of leukemia cases by cell type. Acute lymphocytic leukemia (ALL) represents 79% of the participating cases, acute myelogenous leukemia (AML) represents 16% of total cases, and chronic myelogenous leukemia (CML) represents 5% of the total cases. Both case families that refused to participate were those of cases diagnosed with ALL.

Table 5 illustrates the distribution of childhood leukemia cases by age category at diagnosis. Nine children, representing 47% of the participating cases, were four years old or younger at diagnosis. Four children, three of whom participated in the study (16% of the participating cases) were between five and nine years of age. Seven children of which six children (32% of the participating cases) were between the ages of ten and fourteen years of age at diagnosis. One child, representing approximately 5% of total participating cases, was between fifteen and nineteen years of age at diagnosis.

Exposure to Wells G and H Water

Exposure is based on cumulative exposure values from the Murphy water distribution model. For the time period of exposure before conception, the exposure index illustrating total exposure among cases was between 0.00 and 20.84, while for controls the range was between 0.00 and 11.68. During pregnancy, case exposure indices ranged from 0.00 to 9.21. Control exposure indices ranged between 0.00 and 3.88. For cases, the index illustrating total water exposure from birth to diagnosis was between 0.00 to 25.66. For controls the index ranged from 0.00 to 51.07. Table 6 presents the frequency of cases and controls by exposure to Wells

G and H where cumulative exposure has been dichotomized to illustrate those persons potentially either ever exposed or never exposed to water from Wells G and H. Four cases and thirteen controls did not receive any exposure from Wells G and H at their residence for the entire etiologic period. Fifteen cases and twenty-four controls had the potential to receive at least some exposure to Wells G and H through public drinking water based on the same criteria. Controls had a greater percentage of persons never exposed than exposed for all exposure time periods. Cases always had a greater percentage of exposed individuals than controls. These differences are most pronounced in the exposure time period during pregnancy.

Frequencies are also presented for each of the three time periods of concern throughout the etiologic period of the case; maternal exposure to Wells G and H during the two years before conception only, maternal exposure which occurred during the pregnancy, and the independent exposure the child received during development between birth and the case leukemia diagnosis. For the time period during two years before conception approximately 42% of the cases and 32% of the controls received at least some exposure to water from Wells G and H. Average weekly exposure values for cases and controls (Table 7) ranged from 0.00 to 0.20 for cases and from 0.00 to 0.11 for controls. During pregnancy, approximately 47% of cases and 32% of controls received at least some exposure. Average weekly exposure values ranged from 0.00 to 0.23 for cases and from 0.00 to 0.10 for controls. From birth to diagnosis more than 63% of cases and more than 56% of controls received at least some exposure and average weekly values ranged from 0.00 to 0.14 for cases and from 0.00 to 0.07 for controls.

Table 8 presents the odds ratios that describe the relationship between case-control status and exposure. In all odds ratio analyses, study subjects not exposed are used as a reference point for statistical comparison and thus are considered to have an odds ratio of 1.00.

The odds ratio for the exposed subjects is calculated relative to the comparison odds ratio of 1.00.

The first column of odds ratios presented are unadjusted and therefore potential effects of suspected risk factors, in addition to the water exposure, may be contributing to the results. For the full etiologic period, cases are nearly twice as likely as their matched controls of having the potential for exposure to water from Wells G and H with an odds ratio (O.R.) of 1.99 though confidence intervals (C.I.) for this statistical analysis are wide and not significant (C.I. = 0.52, 7.71). For these results to be considered statistically significant the lower confidence interval would have to be 1.0 or greater. The narrower the confidence interval, the more likely the odds ratio truly represents the amount of risk among cases relative to controls.

Further down the same column we examine the relationship between case-control status and Wells G and H water exposure separating the etiologic period into three individual periods of time. As Table 6 indicates, for the period limited to two years before conception eight (42.1%) case mothers and 12 (32.4%) controls could have been exposed to water from Wells G and H. Table 8 indicates an unadjusted odds ratio of 1.77 (C.I. = 0.39, 8.00) for these people. During the pregnancy, nine cases and 12 controls had the potential for exposure to water from Wells G and H. Unadjusted results indicated that cases were 5.70 times more likely than controls to have been exposed to some degree (C.I. = 0.67, 48.25). The period from birth to diagnosis had 12 cases and 21 controls potentially exposed. Unadjusted rates showed cases only slightly more likely than controls to be at risk of leukemia (O.R. = 1.36, C.I. = 0.00, 5.38).

As mentioned in the methods section, we collected information at interview that allowed for the assessment of the role of known potential risk factors for leukemia and their effects on the results of the water exposure analysis. As will be discussed below, we attempted to control

the data for the effects of five main confounding variables. The variability in a statistical model can become extensive when the model considers the exposure variable and a large number of potential confounders (covariates) run simultaneously on a small study population. Such a situation exists in this analysis as the number of cases is relatively small and there are a fair number of potential confounders to consider. The variability of the model is reflected by the width of the confidence intervals that serve as an indicator of the strength of the odds ratio as a true measure of the relative risk.

As described in the methods section we attempted to statistically adjust for this variability by using a single composite covariate to account for the effects of the five main confounders considered, and to minimize the model's variability (Tukey, 1991). The extent to which the composite covariate is effective in this regard will be illustrated later in the results.

The second column of odds ratios in Table 8 were derived when potential confounders were controlled for in the statistical analysis using the composite covariate. Odds ratios were again calculated for the overall etiologic period and for each of the three components of the etiologic period. Composite covariates were used to control for the effects of socioeconomic status, maternal smoking during pregnancy, maternal age at birth of child, and maternal alcohol consumption during pregnancy. Odds ratios increased for the overall etiologic period (O.R. = 2.39, C.I. = 0.54, 10.59), for the period 2 years before conception, (O.R. = 2.61, C.I. = 0.47, 14.37) and for the period of exposure during pregnancy (O.R. = 8.33, C.I. = 0.73, 94.67). For the time period from birth to diagnosis, the odds ratio decreased relative to the unadjusted value (O.R. = 1.18, C.I. = 0.28, 5.05).

These odds ratios, although not statistically significant, suggest that the relative risk of developing childhood leukemia was greater for those children who were exposed to water from

Wells G and H from their mothers' consumption of water particularly during pregnancy. Odds ratios suggested only slight elevations in risk for exposure during the etiologic period overall and for maternal exposure in the two years prior to conception. No such relationship was identified in the time period between birth and diagnosis. This suggests that the children's consumption of water after their birth had little or no effect on their later development of leukemia.

Given that the odds ratios for exposure during pregnancy were higher than those for the other time periods, it was decided to stratify the pregnancy time period into trimesters in an attempt to identify the trimester of pregnancy in which Woburn water had the strongest effect on leukemia incidence. Table 9a presents the results of these analyses.

When exposure during the pregnancy is divided into trimesters, the unadjusted odds ratios continue to be elevated with effects identified in the second (O.R. = 5.70, C.I. = 0.66, 49.20) and third (O.R. = 7.03, C.I. = 0.83, 59.53) trimesters greater than or equal to effects identified for the pregnancy overall as seen in Table 8.

Odds ratios are also presented which are controlled for the influence of confounders using a composite covariate. The odds ratios are once again adjusted for effects of socioeconomic status, maternal smoking during pregnancy, maternal age at birth of the child, and maternal alcohol consumption during pregnancy. Controlling for effects of these variables increases the odds ratios in the first (O.R. = 3.25, C.I. = 0.47, 22.65) and second (O.R. = 7.54, C.I. = 0.70, 80.77) trimesters but not in the third (O.R. = 6.82, C.I. = 0.77, 60.08). No statistic reached the point of significance. Confidence intervals for these analyses are wide, indicative of few numbers of cases and controls exposed during specific trimesters of pregnancy.

Although we adjusted for the effects that potential confounders might have had on the relationship between disease and exposure status, we were also concerned regarding residual exposure effects from neighboring time periods. In table 9A, for example, we would want to be sure that adjusted odds ratios for each trimester demonstrate effects of exposure which occurred in that specific trimester alone and did not represent residual effects from a previous trimester or overlapping effects of a subsequent trimester.

It was thought that in assessing the risk of leukemia from exposure in one trimester we could control for the effect of the other two by treating trimester as if it were a confounding variable. However, if one trimester was associated or correlated with another, treating trimester as a confounder would not be appropriate. Therefore, in order to assess the degree to which the exposure values for one trimester are associated with the exposure values of another trimester we calculated correlation coefficients.

Table 9B presents the correlation coefficients between water exposure values and trimester of exposure. The correlation coefficients between trimesters are all greater than 0.6 indicating a high degree of correlation between trimesters particularly when the interaction between the second and third trimesters is assessed (correlation coefficient = 0.84). This relationship does not exist between the larger time periods that compose the entire etiologic period presented in Table 8. Correlation here ranged from between 0.17 and 0.54 for time periods before conception to case diagnosis. When the high correlation associated with trimesters of exposure were considered, it was decided to abandon further analyses at the trimester level as interpretation of specific effects for each trimester could not be made with confidence.

As a result of the elevations in odds ratios identified in Table 8, analyses were performed to address the potential for a dose-response relationship associated with water exposure. Trichotomous parameterization was performed (as discussed in the methods section) as shown in Table 10. Exposure score categories for all exposure time periods are defined either as "Never", "Least", or "Most" exposed. The "Never" category indicates no possible exposure to the contaminated water based on the prediction of the Murphy Model, "Least" indicating the least exposed among exposed subjects as defined by the criteria described in the methods section, and "Most" indicating the highest exposure category according to the same criteria.

The actual exposure score values represented in each category are as follows: in all categories, "Never" is defined as an exposure score of 0.00. From two years before conception to case diagnosis, the least exposed have an exposure score no greater than 2.94. Person whose exposure score is greater than 2.94 are considered most exposed. During 2 years before conception, the least exposed have an exposure score no higher than 0.88, those subjects with a higher score are considered most exposed. From birth to diagnosis the least exposed have an exposure score no higher than 1.61, those higher are considered most higher than 0.38, those higher are considered most exposed.

Results of analyses for exposure score categories for the entire etiologic period and each of the three exposure time period sub-categories are presented in Table 11. Exposure during pregnancy demonstrates the highest odds ratios by level of exposure among each of the etiologic time periods as well as for the entire etiologic period overall. The "Least" category had a slightly elevated odds ratio relative to the "Never" exposure level when unadjusted odds ratios were examined (O.R. = 2.36, C.I. = 0.20, 28.48) and rose to an odds ratio of 3.53 (C.I. = 0.22, 58.14) when adjusted for confounding. Results are not statistically significant and fairly wide

confidence intervals are indicative of the fewer number of cases and controls per category. Those subjects at the highest exposure level demonstrate a much higher odds ratio relative to the least exposed. The most exposed category had a lower end confidence limit which came close to statistical significance (O.R. = 14.00, C.I. = 0.98,195.60) for the unadjusted and an odds ratio of 14.30 (C.I. = 0.92, 224.52) for the adjusted. The width of the confidence interval was once again indicative of the small number of subjects in each category. A statistical test for trend across exposure categories was significant for the period during pregnancy ($P<0.05$) suggesting a dose-response relationship between water exposure and childhood leukemia for exposure that occurred to the fetus during pregnancy.

The birth to diagnosis exposure category odds ratios were not highly elevated, as they remained below 2.50 for both unadjusted and adjusted analyses and all exposure levels. For the period of time two years before conception, adjusted odds ratios were highest for the higher exposure category (O.R. = 2.82, C.I. = 0.30, 26.42) but were not nearly as high as identified for other exposure time periods. There was no evidence of a trend toward increased risk with increased exposure for these two time periods.

As previously discussed, the small sample size of the study was a concern with regard to the confidence of the statistical analyses. Statistical tests resulted in odds ratios with wide confidence intervals due to the small sample size. In an effort to narrow the confidence intervals of the statistical tests without compromising the accuracy of the point estimates, a composite covariate was created as explained in the methods. Table 12 illustrates differences in results when data are adjusted by using many covariates in the logistic regression model versus using a single composite covariate to represent confounders. The first set of odds ratios are those generated using a composite covariate and are the adjusted odds ratios previously presented in

Table 8. The second are odds ratios generated by running a logistic regression that includes a term for each of the potential confounders.

Differences in odds ratios for each time period are unremarkable with the exception of the time period representing overall exposure during the pregnancy. Here use of the composite covariate has resulted in an odds ratio below that of the all-covariate model. Confidence intervals are narrower than those resulting from use of all the covariates.

Considering that study findings were suggesting an association between the risk of leukemia and receiving water from Wells G and H, it was important to determine if exposure took place through consumption of the water. At interview, residential history information collected included a question that asked for the primary beverage type of the mother prior to the child's birth and that of the child after the child was born. We conducted analyses to determine if there was a relationship between considering public water as the primary beverage and being diagnosed with childhood leukemia.

To simplify the analysis, the single residence where the mother and child lived the longest was considered the primary residence and therefore the primary beverage reported for that residence was considered the primary beverage consumed. As a univariate, the relative risk of consuming public water as the primary beverage and being diagnosed with childhood leukemia was 3.03 (C.I. = 0.82, 11.28), an odds ratio which is elevated but not statistically significant.

When the relationship between cumulative water exposure and leukemia risk originally presented in Tables 6-11 is reexamined and the primary beverages consumed for each subject are considered in the statistical relationship, the information in these tables remains virtually unchanged.

Seventeen of the twenty-one cases were diagnosed as having acute lymphocytic leukemia (ALL). The two-case refusals both had acute lymphocytic leukemia. Limiting the analysis to the remaining fifteen ALL cases alone lowered the odds ratio for exposure during the entire pregnancy to 2.86 (C.I. = 0.30, 27.22) from an odds ratio of 5.69 (C.I. = 0.66, 49.20) (Table 13). Although the strength of the association is somewhat decreased among ALL cases alone, elevated odds ratios still suggest a relationship between the exposure metric and leukemia incidence during pregnancy.

Analysis of Other Possible Risk Factors

The childhood leukemia questionnaire was designed to collect information concerning suspected risk factors for childhood leukemia and residential data for the purpose of establishing an accurate Wells G and H exposure metric. Our analyses examined each of these factors and how they affect relative risk. Many questions received too few positive responses for meaningful analysis. A general outline of question categories will be presented. Statistically significant results for questions with a total of 10 or more positive responses among cases and controls whose results are statistically significant will be presented.

Demographic information focused primarily on race, religion, and socioeconomic status of the study subjects. Information concerning race and religion was collected at interview, while socioeconomic information was generated using Hollingshead's two factor index of social position (Hollingshead, 1958). Neither race, religion, or socioeconomic status demonstrated statistically significant associations with leukemia incidence.

Residential History

The residential history included information pertaining to the pesticide use, passive smoking, and miscellaneous sources of fumes and odors. Small numbers of positive responses

to the home environmental questions precluded analyses for these variables. Passive smoking results will be discussed as part of the overall smoking analysis.

Occupational History

The occupational history analyses were performed using two approaches. The first approach was to review the occupational data from an a-priori perspective, examining the data in a method that addresses those industries and jobs where exposures may occur which have been identified as potentially associated with increased cancer incidence. The second involved an aposteriori approach, examining the data specific to greatest frequency of the industry and job types reported at interview and potential associations based on those occupations most reported. It is important to remember that in this study, analyses address the occupational exposures of parents of subjects. In all instances, subjects themselves were too young for employment prior to the date of diagnosis.

If one parent is unavailable for interview, the other parent may complete an occupational history for both parents. This results in less reliable information regarding occupational exposures for the missing parent. In this study, in the majority of the circumstances, 79% of cases and 89% of controls, each parent responded regarding their occupational history themselves, hopefully providing a good first-hand sense of potential occupational exposures.

Because we were able to interview most parents directly about their exposure we were able to classify each study subject parent based on the type of industry the person worked for and the specific job they performed within that industry (Classified Index of Industries and Occupations, 1982).

For the a-priori analysis, the occupational data was stratified by industries and occupations which previously have been identified as high risk based on their potential for

hazardous exposures or previous statistical associations. Appendices XIII and XIV list the industrial and occupational categories that have been considered high risk (Savitz 1990). Table 14 presents a summary of work history analysis for each parent by industry and occupation. For all mothers employed in industries considered high risk, no association was seen between working at this job and childhood leukemia incidence (O.R. = 0.79, C.I. = 0.24, 2.57). For mothers who reported occupations considered high risk, again no association between maternal occupation and leukemia incidence was identified (O.R. = 0.71, C.I. = 0.19, 2.82).

Fathers who reported having worked for industries considered high risk had an elevated but not statistically significant likelihood of having a child with leukemia (O.R. = 2.55, C.I. = 0.78, 8.30). Fathers who reported working in a high-risk occupation did not show this relationship (O.R. = 0.75, C.I. = 0.13, 4.47).

Despite the availability of detailed occupational information for study subjects the small study population size restricted the number of industry and occupational analyses which could be performed. Tables 15 and 16 demonstrate the distribution of subject mothers and fathers among industry category. Given that the current economy of Woburn and its surrounding communities is primarily industrial, it is not surprising that a high percentage of fathers, 40% of case fathers and 32% of control fathers, are employed in the durable or non-durable goods manufacturing industry. The majority of mothers (40% of cases and 28% of controls) were employed in the professional and related services industries. This would include working in doctors' offices, schools, libraries, and other professional office settings. Table 17 presents relative risk by industry category for those industries in which at least 10 subjects (cases and controls in total) reported employment. In no instance was the mother's industry category associated with childhood leukemia incidence. Among fathers, the durable goods manufacturing

industry demonstrated an odds ratio of 1.93 (C.I. = 0.63, 4.72). No occupational analysis among industries most reported in employment histories demonstrated an association with childhood leukemia.

Tables 18 and 19 present the distribution of parental occupations by occupation category. Table 18 presents the odds ratios for categories for which at least 10 subjects reported employment. The majority of mothers who worked outside the home performed support occupations (33.3% of case mothers and 21.8% of control mothers) while 55.6% of case mothers and 52.7% of control mothers were homemakers. Fathers were fairly evenly distributed throughout the paternal occupational categories. Once again, odds ratios demonstrate no association between occupational categories most frequently reported and childhood leukemia incidence.

Occupational exposures and their relationship to health effects among women have received much less attention in the literature than those among men as women have traditionally been less likely to work in occupations with potentially hazardous exposures. This pattern of occupational history was seen among our data as well (Table 20). For mothers, the strongest evidence for childhood leukemia has been among pharmacists, and mothers working in industries involving metal processing, textile manufacturing, pigments, and chemical processing.

Table 21 presents the results of interview questions concerning chemical exposures at work. Each parent was asked specifically about exposure to certain chemicals identified as potential risk factors for leukemia (Linet, 1985) at any time during their working life. Mothers of cases reported only three work related chemical exposures, one each for chloroform, pesticides, and herbicides. Mothers of controls also reported relatively few occupational exposures to chemicals, five reported occupational exposures to pesticides, one each reported

exposure to chloroform, ionizing radiation, and herbicides, and three reported a general exposure to solvents.

Table 21 also shows that among fathers, there was a wider dispersal of reported chemical exposures than among mothers. The majority of reported exposures among case fathers was for general solvents (nine reported exposures), lead (five reported exposures), and trichloroethylene (four reported exposures).

Among fathers of controls, again a wide distribution of chemical exposures was reported. In 21 instances exposure to general solvents was reported, 13 control fathers reported exposure to lead, ten to carbon tetrachloride and eight to polyvinyl chloride. At least two control fathers reported exposure to each chemical referred to in the questionnaire.

Only fathers reported use of certain chemicals frequently enough for statistical analysis (total responses for cases and controls were 10 or greater). These chemicals included lead, polyvinyl chloride, carbon tetrachloride, trichloroethylene, and for other nonspecific solvent use. In all instances odds ratios were below 1.00 and ranged between 0.43 and 0.82 indicating no association between reported chemical exposure at work and being the father of a case.

Study Subject Medical History

Appendix XV describes the frequency of health conditions which were identified as part of the medical history information collected on study subject children specific to the time frame prior to case diagnosis. Parents were asked if children had infections, mononucleosis, allergies, asthma, chicken pox, rubella (German measles), rubella (measles), mumps, a shigella infection, a salmonella infection, aplastic anemia, a cytomegalovirus infection, a urinary tract infection, or cancer. Positive responses were too few for statistical analysis. Control parents reported that none of the control children had been diagnosed with any form of cancer.

Parents were questioned concerning the diagnosis of birth defects among study subjects as listed in Appendix XVI. They were questioned concerning Down's Syndrome, Bloom's Syndrome, Klinefelter's Syndrome, X-linked agammaglobulinemia, Ataxia Telangiectasia, and Wiskott-Aldrich Syndrome. No subject was positively diagnosed with any of these congenital anomalies.

Parents of study subjects reported no transfusions among any study subjects prior to case diagnosis. Questions concerning children's immunization history were not considered for analysis as greater than seventy percent of parents could not provide immunization information.

Maternal Pregnancy History

Increasing maternal age at study subject birth has shown no association with leukemia incidence in this study (O.R. = 0.55, C.I. = 0.14, 2.07). It has been considered however as a component of the composite covariate analysis so as to account for any potential effect it may have on the final outcome. Information concerning birth order of the study subjects revealed no relationship between birth order and childhood leukemia. Analysis for birth order trend revealed a chi square of 0.29 (P = 0.59). Parents were questioned concerning the incidence of birth defects among siblings of study subjects. None of the nineteen cases whose families participated in this research project were reported as being diagnosed with birth defects. One control was reported diagnosed with an eye disorder.

Information was also gathered regarding birth defects among siblings of study subjects. Only one case family reported birth defects among case siblings. This family reported two siblings diagnosed soon after birth with congenital hernias.

Among controls, five families reported a total of seven study subject siblings as having been diagnosed with birth defects. The family that reported the control as having an eye

disorder also reported that three other children in their family were diagnosed with the same disorder. One control family reported a sibling with a renal disorder coupled with musculoskeletal disorder. Three other control families reported one birth defect per family; a mental disorder, a musculoskeletal disorder and a heart anomaly.

Among the birth defects reported, the congenital hernias and eye disorder were familiarly aggregated. The remaining birth defects predominantly represent birth defect categories of different organ systems. No reason for them to be linked to environmental cases is apparent.

Questions concerning employment outside the home immediately before and during pregnancy demonstrated a non-significant elevation in risk associated with working outside the home in the three months before the pregnancy. This relationship was not seen when employment by trimester was examined (Table 23). Case mothers were more likely to be employed during the three months prior to conception than mothers of controls (O.R. = 1.57, C.I. = 0.47, 5.46). This relationship was reversed after the pregnancy began as case mothers were less likely to be working than control mothers for all three trimesters of the pregnancy.

We examined the potential effects of smoking on the children both from in-utero exposure for mothers who smoked while pregnant and from potential exposure to passive smoke from household members who smoked in the home after the child was born up until the case diagnosis. Eight cases and 17 controls had at least one smoker living in the household at some time during the etiologic period. No association was identified between smokers living in the home during the etiologic period and the occurrence of childhood leukemia (O.R. = 0.53, C.I. = 0.12, 2.35).

When the association between maternal smoking during pregnancy is examined, 6 control mothers and no case mothers stated that they had smoked during pregnancy. No association was identified between smoking during pregnancy and childhood leukemia.

Mothers were questioned regarding their use of contraceptives in the three months prior to their pregnancies with the study subjects. Positive responses in one case mother and two control mothers were too few to allow for analysis.

Each mother was questioned concerning beverage intake during pregnancy. It was determined that all case and control residences pertinent to the study received Woburn public water. All case and control mothers reported drinking tap water and beverages made from tap water during pregnancy. This information validates the use of the Murphy Water Model to assign indices for Wells G and H water exposure to all study subjects during their gestational period.

Alcohol use during pregnancy was also examined. Ten case mothers and 15 control mothers stated they consumed some amount of alcoholic beverages during their pregnancy. These mothers stated their alcohol consumption was limited to beer or wine only. They drank no more than one drink per week or less. Matched analyses comparing those who drank some alcohol to those who did not indicated a slight non-significant elevation in risk of leukemia and alcohol consumption (O.R. = 1.5, C.I. = 0.54, 4.20). The small number of positive responses precluded an assessment of a dose-response relationship between alcohol use during pregnancy and disease incidence.

Mothers were questioned concerning specific illnesses they may have experienced or specific medications they may have taken during their pregnancies. All respondents said they had not experienced any of the illnesses or taken any of the medications as listed in Appendix

XVII throughout their pregnancies with the study subjects. No mother reported any other illness during pregnancy.

Ten mothers reported breast-feeding the study subjects after delivery, seven were case mothers, three were mothers of controls. This resulted in a significant association between breast-feeding and leukemia diagnosis (O.R. = 10.17, C.I. = 1.22, 84.5). There were only a total of ten positive responses to the breast-feeding question, however, which accounts for the large confidence intervals.

Mothers were questioned regarding specific medications which were suspected in the literature to be associated with childhood leukemia if consumed during pregnancy (Linet, 1985). Appendix XVII lists these medications, none of which were consumed by any mother during the pregnancy. No mother reported illicit drug use at any time 3 months before or during the pregnancy.

Mothers were also questioned concerning diagnostic procedures that required radiation exposure during pregnancy. Appendix XVIII lists these procedures, none of which were reported performed on study subject mothers.

Questions concerning dental X-rays reveal that six case mothers had dental X-rays during pregnancy while two control mothers had a similar procedure. Matched analysis revealed an odds ratio of 10.49, (C.I. = 1.26, 87.1). Of these, five case mothers reported that they were unsure if a lead shield apron was used to shield them from abdominal exposure to X-ray. The remaining case and control mothers did not report the use of lead shields.

Four cases and seven controls reported that they were administered anesthetics three months prior or during the pregnancy for use during a medical or dental procedure other than

associated with the delivery of the child. There was no association between anesthetic use and occurrence of childhood leukemia (O.R. = 1.21, C.I. = 0.28, 5.07).

Questions were asked specific to the use of chemicals in the home three months prior to or during pregnancy. No mother reported use of pesticides or herbicides during this time period. Five cases and 17 controls reported their use of oven cleaners during the pregnancy. No association was found between oven cleaner use and leukemia incidence (O.R. = 0.48, C.I. = 0.38, 1.79).

During the design of this questionnaire, the beginnings of interest in the effect of 60 Hz EMF had surfaced in the literature. At that time we inserted questions in the questionnaire to probe for common home sources of exposure to 60 Hz EMF. We asked mothers if they used either a heating pad or electric blanket on a regular basis during pregnancy as these devices are held close to the body during use and have been identified as potential sources of 60 Hz EMF. We also asked for information concerning when during the pregnancy mothers used either item. Only one case mother reported using a heating pad during the etiologic period, no one reported using an electric blanket.

60 Hz EMF

As described in the methods section researchers used residential information collected during the interview to conduct a field survey of power line configurations in the neighborhoods which the cases and controls resided. The fifty-six study subjects lived in ninety-one separate addresses (many residents lived at more than one address during the etiologic period) for which information was collected during the interview process. Of the eighty-five Woburn addresses identified, seventy-three were successfully wire coded based on the Kaune version of the Wertheimer-Leeper wire coding scheme (Kaune, 1994). Twelve addresses could not be wire

coded. Four residences no longer existed, and eight residences corresponded to units in apartment complexes and were not amenable to coding.

Forty-six of the seventy-three study subject addresses (63%) were classified as having an ordinary low current configuration (OLCC). Of the nineteen eligible case addresses, fourteen were OLCC (73.7%) and of the fifty-four eligible control addresses, thirty two were OLCC (59.2%). Due to the fact that so few study subject addresses fell into the highest and lowest current configuration categories (18%), analyses were performed by collapsing the very high current configuration (VHCC) and ordinary high current configuration (OHCC) categories into a single high current configuration (HCC) category and the ordinary low current configurations (OLCC) and very low current configuration (VLCC) categories into a single low current configuration (LCC) category (Table 24). An analysis for linear trend in proportions was not significant ($p = 0.60$).

The most definitive analysis for the identification of health effects based on wire code is of the subgroup of cases and controls who had resided in the same household for the entire etiologic period. These subjects would receive all residential EMF exposure at a single address. The surrogate wire code value is assured to be the appropriate value for the entire etiologic period for all study subjects.

Thirty-nine of the seventy-three subject addresses were considered a stable address (Table 26). This represents 15 cases, 79% of the case population, and 24 controls, 44% of the control study subjects. As stable subjects have, by definition, one unique address for the entire etiologic period, their residential data is amenable to matched analysis. Among the stable subjects, a matched (HCC vs. LCC) analysis revealed an odds ratio of 2.20 (C.I. = 0.37, 13.11).

Other Risk Factors

We further asked specific questions regarding exposure of the child to electric blankets, heated water beds, or heating pads from birth to diagnosis of the case. One case was reported to have used a heating pad during the etiologic period. No cases used electric blankets or heated water beds. No controls used any of these electric devices. Few positive responses precluded analysis of this data.

Questions regarding cancer incidence among immediate family members were asked. We were concerned about cancers among maternal and paternal grandparents, either parent or any sibling of the study subject. Sixteen subject families, 8 case families and 8 control families reported that a paternal grandfather had been diagnosed with cancer although there was a wide distribution of cancer types. An elevated non-significant association was identified between the diagnosis of cancers among paternal grandfathers and occurrence of childhood leukemia (O.R. = 2.01, C.I. = 0.73, 5.58).

The final section of the questionnaire focused on environmental exposures that may have occurred during activities both inside and outside the home. When information concerning the schools attended by each study subject was examined the data indicated that cases were not more likely to attend a specific school in Woburn than matched controls. We then asked specific questions concerning subjects hobbies and activities. The most common activity identified among subjects was fishing. Six cases and 12 controls were reported as having fished in a body of water within Woburn (O.R. = 1.0, C.I. = 0.27, 3.71). In no instance was there a relationship between childhood leukemia and participation in hobbies or indoor and outdoor activities that would have taken place in Woburn. There was no relationship between the use of specific

recreation areas and disease incidence. Cases were also not more likely than controls to be exposed to cats or farm animals.

There was also no relationship between childhood leukemia and fathers' military service history. Only one subject father served in Vietnam.

DISCUSSION

The pattern of childhood leukemia incidence in Woburn has changed dramatically in recent years. Rates of leukemia have been elevated since the early 1970's. Cases diagnosed between 1969 and 1979 demonstrated a residential distribution of close geographic proximity within the eastern part of the city. From late 1979 until 1986 the increased incidence continued but with a more even geographic distribution throughout Woburn. City water supply Wells G and H were discovered to be contaminated and closed in late 1979 but new incident cases of childhood leukemia continued to be diagnosed for more than seven years. From mid 1986 to early 1994 there had been no new diagnoses of childhood leukemia in Woburn. Two new cases were diagnosed; one each in February and March of 1994 among Woburn residents. The leukemia rates in Woburn are approaching expected levels over time as observed incidence in recent years has been below normal.

It is clear that between 1969 and 1986 leukemia was being diagnosed among children in Woburn at a significantly elevated rate. The patterns of incidence over time (including a very long time period between mid 1986 and early 1994 when no new childhood leukemia cases were diagnosed) allows for a variety of arguments in explanation of the patterns of incidence. It can be argued that although Wells G and H were closed in 1979 the leukemia diagnoses which

occurred after their closure were outcomes which were potentially initiated while the wells were still in use.

The original study conducted by the Massachusetts Department of Public Health was performed to explore potential causes of increased incidence of childhood leukemia, renal cancer, and liver cancer in Woburn. Analysis if the data was performed by the MDPH in consultation with the CDC. The expected number of incident cases for each of the diseases was calculated using age and sex-specific incidence data from the Third National Cancer Survey (TNCS).

An analysis of residence at the time of diagnosis of the leukemia cases from the 1981 study showed a concentration of cases in the eastern part of Woburn. Six cases resided in one census tract in East Woburn in an area of approximately a 1/2 mile radius. There was a statistically significant concentration of cases in this census tract; the probability of 59% or more of the 12 cases occurring in this area, which contains only 17% of the town's 0-14 age group population, is less than 0.01. The observed number of cases in this census tract was significantly higher than expected based on the TNCS. Childhood leukemia incidence for the rest of Woburn was not significantly elevated compared to national rates. The overall elevation for Woburn as a whole was accounted for primarily by the elevated rate in one single census tract.

The researchers addressed a significant part of their analysis on the proximity of case residences to areas of known environmental contamination in Woburn. They demonstrated that the majority of the childhood leukemia cases were statistically significantly more likely to be in a census tract where residences were closest to known environmental contamination and most proximal to Wells G and H. A near/distant control matching scheme was employed to allow for

the ability of case comparison to two control groups which differed based on the proximity to known sources of potential environmental exposure.

Results of the 1981 leukemia investigation were : (1) the incidence of childhood leukemia in Woburn was significantly elevated for the period 1969 - 1979 (12 cases observed, 5.3 cases expected); (2) the excess leukemia cases were found primarily among males, not females; and finally (3) there was a concentration of cases in the eastern part of Woburn.

The fundamental differences between this study and the first are 1) the larger number of study subjects due to the continued elevation in incidence of childhood leukemia through 1986 (21 vs. 12 cases) 2) more specific information was available regarding environmental exposures and rates of exposure in Woburn, specifically with the application of the refined water distribution model to allow for the generation of an exposure metric 3) comprehensive occupational, residential, and health history data not fully available with the first study and 4) Electric power distribution line data specific to study subject residences in Woburn for the assessment of 60 Hz EMF exposure among cases and controls.

The most important difference between the present MDPH study and the 1981 study is the application of the Murphy water distribution model to the residential history information. The cases could be analyzed with more sensitive analyses than available before to assess the association between potential exposure and outcome. The current work serves as a refinement of the previous work to better address associations whose relationships were limited given the small study population and the absence of reliable data for exposure assessment.

The specificity of the Wells G and H water exposure values allowed for the assessment of potential associations between water exposure and leukemia throughout the children's residential period in Woburn. Table 6 presents frequencies of exposure in the overall etiologic

period and for substrata of the etiologic period. Exposure information is based on ever being exposed vs. never being exposed to water from Wells G and H.

Table 8 presents the odds ratios for the relationship between leukemia and exposure during the overall etiologic period. Total exposure for this period (from two years prior to conception until case diagnosis) shows a weak non-significant association with leukemia incidence. Maternal exposure during the two years prior to conception demonstrates about the same risk.

Strikingly however, the adjusted odds ratio for maternal exposure during pregnancy suggests that the risk of developing childhood leukemia was greater for those children whose mothers consumed water from Wells G and H during pregnancy than for those whose mothers did not. In contrast, odds ratios suggest that the relative risk of developing childhood leukemia among children who consumed water from Wells G and H from their birth through childhood was virtually identical for cases and controls. This means that the cases' consumption of contaminated public water as children was not associated with their subsequent development of leukemia. A mother's consumption of contaminated public water while pregnant with the case was the strongest predictor of childhood leukemia incidence.

Table 9a presents the results after further sub-stratification of the pregnancy exposure time period. Elevated unadjusted odds ratios are seen particularly in the second and third trimesters. Correlation coefficients presented in Table 9b demonstrate high correlation in exposure between each trimester. As a result, these data then cannot be effectively used to make distinctions between trimesters with regard to relationships between exposure by trimester and disease outcome.

Potential dose-response relationships were assessed by performing a trend analysis based on the distribution of exposure values as illustrated in Table 10. Exposure values were divided into three categories based on an even division of the exposed population as described in the methods section of this report.

The results presented in Table 11 demonstrated the strongest relationship to exposure for the highest exposure category during the pregnancy time period. Odds ratios for the most highly exposed study subjects demonstrate an estimate that the relative risk of developing childhood leukemia among cases was greater for those subjects whose mothers consumed water from Wells G and H than those who did not. Results are not statistically significant but the lower confidence interval suggests borderline statistical significance in both unadjusted and adjusted estimates. Although confidence intervals are extremely wide for odds ratios of individual pregnancy strata, a test for trend is significant, suggesting the existence of a dose-response relationship between Wells G and H water and childhood leukemia for exposure during pregnancy.

To further validate the findings, we evaluated the relationship between Wells G and H and leukemia according to whether or not individuals reported using their tap water for consumption. During obtainment of residential history, parents confirmed that the residences in question all received Woburn public water. We also asked parents if the primary beverage consumed by the subjects was tap water or a beverage made from tap water or likely to be a store-bought beverage. Parents reported that leukemia cases were three times more likely to have tap water or beverages made from tap water as their primary beverage than their matched controls. This result is consistent with our findings that cases were more likely to be exposed to water form Wells G and H than matched controls. The subjects' consumption of tap water

during childhood serves here as a surrogate indicator of tap water consumption by the mother during pregnancy. The tap water question must be interpreted with caution however as respondents were likely to be aware of the community's concerns regarding ill health and exposure to contaminated public water.

The children's consumption of tap water would be indicative of the time period from birth to diagnosis, the segment of the etiologic period identified as having the weakest association between case-control status and exposure. Although cases were three times more likely to consume tap water than controls, the Murphy water model has demonstrated that the consumption of tap water alone is not sufficient for exposure. Exposure is related to water consumption at specific time periods during the operation of the wells. Without considering the specific time period of water consumption, exposure cannot be assessed.

Most results on the relationship between leukemia and exposure to Wells G and H water during pregnancy suggested an association but were not statistically significant. The risk estimates obtained were bounded by wide confidence intervals indicating that the risk estimate was not especially precise. We attempted to enhance precision by modifying the terms entered into the model utilizing a procedure put forth by Tukey (1991). Table 12 demonstrates a comparison of odds ratios adjusted using a multiple conditional logistic regression model including one term for each confounder and adjusted using a model employing a composite covariate as discussed in the methods section.

Although the Tukey analyses reduced the width of the confidence interval about the point estimates, small numbers of subjects continue to demonstrate the imprecision of the statistical calculations. Adjustment using the Tukey method does not change the direction or

pattern of the identified associations. The magnitude of the risk estimates must be interpreted with caution.

Normalization of Exposure Scores

As a method of addressing the variability in exposure values that exist among exposure categories, exposure was assessed using normalized exposure scores for subjects representing exposure per unit time. Average monthly exposure values were generated for the exposure period associated with the time of the pregnancy as exposure during this time period has demonstrated the strongest association with disease outcome. Average weekly exposure values ranged from 0.00 to 0.23 for cases and from 0.00 to 0.10 for controls.

Normalization served to narrow the range of potential exposure scores and thus minimize the effect of more extreme exposures and ignore potential commutative exposure effects. Normalized unadjusted odds ratios for exposure during pregnancy resulted in a positive association between disease status and exposure which was greater (0.R. = 9.97, C.I. (1.22, 81.22) than that of the non-normalized (O.R. = 5.70, C.I. = 0.67, 48.25) results. The finding was statistically significant unlike that of the non-normalized results.

Although normalization confirmed the existence and direction of a possible association, the wider normalized confidence intervals suggest the results to be less stable than those of the non-normalization should be interpreted with caution.

Other Risk Factors

One of the other major objectives of this study was to examine the relationship between potential risk factors other than exposure to water from Wells G and H and their potential relationship to the incidence of childhood leukemia in Woburn. When maternal and paternal employment history was examined based on the most frequent industries (Tables 15 and 16) and

occupations (Tables 18 and 19) reported, no significant relationships between childhood leukemia incidence and industry of employment or specific occupation of either parent was identified (Tables 17 and 20).

When industries and occupations considered high risk for carcinogenic exposure (Appendices XIII and XIV) were analyzed (Table 14), only the high risk industry category among fathers demonstrated an elevated but weak relative risk. Categorization of an industry as "high risk" identifies a facility as one that performs a manufacturing process that could possibly place workers at increased risk of cancer incidence due to chemical exposure. Generally, control measures are in place within the work place to limit workers exposure to potentially harmful chemical agents but some level of exposure still may occur.

If a person is identified as working in an industry considered "high risk", he or she may not be directly exposed to the process which contributes to the risk but may instead work at an occupation within the facility which may not be of particularly high risk. If persons are identified as working in a "high risk" occupation, however, they are more likely to be performing their job in the work environment directly associated with the risk and are therefore more likely to come into contact with a carcinogenic chemical agent.

Keeping this in mind, the father's occupational classification that is most indicative of work environment exposures shows no association with adverse outcome. Only the more general occupational classification, which is less predictive of work environment exposure, demonstrates this relationship.

If a true association existed between potential industrial exposure of fathers and childhood leukemia, a similar relationship would be expected specific to the relationship between paternal occupation as a stronger indicator of probable carcinogenic exposure in the work

environment. Although case fathers more often worked in high-risk industries than control fathers, they may not actually have been performing high risk jobs. If case fathers worked for a chemical company, for example, they reported being more likely to perform duties not directly involving chemical contact such as working as a computer programmer or accountant for the company.

Some parents were likely to be exposed to potential carcinogens despite their job descriptions. Table 21 presents the results of the question specifically asking if parents were aware of being exposed to chemicals that could be potentially harmful. There were too few positive responses to consider doses of exposure. Analyses therefore only considered whether parents were ever or never exposed to the listed chemicals at work during the etiologic period.

While mothers had too few positive responses for meaningful analyses, results are presented for fathers' chemical exposures with a total of ten or more positive responses. The results support no association between known occupational exposures among parents and childhood leukemia incidence among their offspring.

Table 22 summarizes the results of the remaining univariate analyses that considered all other information collected from study subject families. Paternal grandfathers of cases were more likely to have been diagnosed with some form of cancer than controls. No specific type of cancer seemed more predominant than the other, however. Whether this weak association relates to childhood leukemia is unclear.

Maternal alcohol consumption during pregnancy was weakly and non-significantly associated with leukemia diagnosis. This variable was used as a component of the composite covariate (Tables 7-11) and did not diminish the effect of the Wells G and H exposure relationship. It does not appear to be a major factor in leukemia incidence.

There was a statistically significant association between having been breast-fed and childhood leukemia incidence. Although the point estimate is significant, very wide confidence intervals reflect the small number of subjects who breast-fed and thus the uncertain strength of the association. The relationship between breast-feeding and childhood leukemia thus remains unclear.

Not shown in the table was a finding regarding dental x-ray consumption. Maternal exposure to dental X-ray showed a statistically significant but unstable association (O.R. = 10.49, C.I. = 1.26, 87.1) because only eight study subjects (6 cases and 2 controls) reported having been exposed to dental x-rays.

No association was identified between smoking during pregnancy and leukemia risk. Although recent findings in the literature suggest an elevated risk estimate for smoking and leukemia (Siegel, 1993), our study allows for the generation of only one risk estimate for this relationship. Our research was not specifically designed to address this issue and conclusions based upon our results for this relationship are not scientifically definitive. Uncertainty regarding this association must be resolved by new investigations designed to address the smoking and leukemia relationship.

While the principal analyses controlled for the effects of those covariates that have been shown to be associated with leukemia in the scientific literature, analyses were also conducted which controlled for only the covariates that demonstrated an association with leukemia for this study (Table 22). Results of each analysis demonstrated adjusted odds ratios which were close to those obtained in the original composite covariate analyses (Table 8). Exposure during pregnancy continued to demonstrate the strongest exposure relationship. This was most evident when results were adjusted for dental x-ray exposure during pregnancy (O.R. = 10.38, C.I. =

0.72, 149.2) compared to the composite adjusted odds ratio value (O.R. = 8.33, C.I. = 0.73, 94.67).

Although the odds ratio is statistically significant, the instability of the statistical calculation demonstrated by the large confidence intervals warns that these results should be interpreted with caution. Adjusting for the main effects that demonstrated the statistical association has shown, however, that the relationship between exposure during pregnancy and disease outcome persists after adjustment for all covariates either plausible as indicated in the literature or possible as demonstrated in univariate analyses.

The strength of our conclusions comes from a detailed exposure model for public water distribution and the consistency in direction of the associations identified (Table 8 and 10). Associations with other risk factors such as breast feeding and dental X-ray exposure cannot be presented with an equal level of certainty as no consistency in direction of association can be definitively established based on single risk estimates.

60 Hz Electric and Magnetic Fields

Our research focused on the assessment of power line configurations according to the Wertheimer-Leeper protocol rather than actual measurements of magnetic or electric fields. Our analysis was further limited by a small sample size that restricted our capabilities to assess the effects of small differences in exposure. Stratification of 60 Hz EMF exposure categories beyond the dichotomous level proved infusible.

Although we did not attempt to determine the correlation between the wire code information we collected and field measurements in participants' homes, the scientific literature has shown wire code configurations did not correlate well with in-home magnetic field values. Studies have, however, demonstrated associations between leukemia risk and wiring

configuration (Savitz, 1990) (London, 1991). The field strengths that may have affected study subjects would have been those present as long as thirty years ago. But the magnetic field strengths measured today would unlikely reflect those present in the distant past. Our assessment, therefore, focused on wiring configuration which is less likely to change over time.

In no circumstance was there a transmission line near enough to a home to be considered in the Wertheimer/Leeper coding scheme. There were also no subjects who resided in homes that had underground power supplies. Previous researchers have assumed study subjects residing in homes supplied by underground wires to have zero exposure and thus are conveniently the referent group in stratified analysis. In our case, with no such sub-population, it was necessary to use, as a reference group, persons who were likely to have some level of exposure.

Comparison with The Harvard Study Findings

In 1983 a study was conducted by Harvard researchers (Lagakos et al., 1986) designed to build on the original MDPH study by assessing a water distribution model which had been prepared by the Massachusetts Department of Environmental Quality Engineering (DEQE), now the Department of Environmental Protection (DEP), designed to predict dispersion of water from the contaminated wells throughout Woburn. This model, derived by Waldorf and Cleary (1984) allowed the Harvard researchers to assign an exposure metric to each study subject based on the subject's address and dates of residence in Woburn.

In addition, the researchers conducted a telephone sample survey of Woburn households that gathered information on adverse pregnancy outcomes and childhood disorders occurring to former and current family members between 1960 and 1982. Surveys were conducted by 235 volunteer interviewers about half of whom were from Woburn and the remainder from nearby

towns or from the Harvard University community. The questionnaire was designed to gather information regarding pregnancies ending between 1960 and 1982 including pregnancy dates, maternal age, and pregnancy outcome, health problems among children, and the residential history of family members.

The researchers merged Wells G and H exposure data with information for the interview and conducted analyses specific to the occurrence of childhood leukemia, perinatal deaths, congenital anomalies, childhood disorders, spontaneous abortions, and low birth weight. They found positive statistical associations between exposure to water from Wells G and H and childhood leukemia, perinatal deaths, two to five categories of congenital anomalies, and two of nine categories of childhood disorders.

Specific to childhood leukemia the researchers assessed information concerning 20 childhood leukemia cases, the 12 from the original MDPH study, 1 case diagnosed before 1969 and not included in the original MDPH study and 7 new cases diagnosed through 1980.

Although the researchers looked at a variety of outcomes as discussed above, discussions beyond the results specific to childhood leukemia are beyond the scope of this document. Researchers found that a statistical association between the occurrence of childhood leukemia and the potential for exposure to water from Wells G and H did exist. They identified both a "cumulative" and an ever/never exposure metric as positively associated with leukemia rates. They felt there were too few cases to definitively conclude which association was the strongest.

The characterization of exposure during specific time segments within the subject's childhood are not presented by Zelen and Lagakos. Their analyses of "cumulative" and "none versus some" exposure metrics are based on summation exposure scores which estimate

exposure on an annual basis. Their method of assigning exposure during pregnancy, for example, includes the pregnancy exposure time segment as part of an annual exposure score. They state "we merged Wells G and H exposure information with other data and assigned to each pregnancy the annual exposure score corresponding to the mother's residence in the year the pregnancy ended" (Lagakos et al., 1986 pp 585-586). The annual exposure score became part of the cumulative exposure values for each subject.

Our exposure data was based on aggregate totals of month by month exposure values for each case and their controls. We were thus able to sum monthly exposure values based on where the mother lived relative to more than fifty zones of exposure during each month of exposure in Woburn. This allowed for the generation of exposure values specific to the months of the pregnancy and the residence or residences the mother lived during the pregnancy.

Zelen and Lagakos computed yearly exposure values based on five zones of exposure in Woburn. They assigned a rate for each year a case resided in Woburn and assigned a similar rate to each non-case that participated in the sample survey. They then calculated cumulative exposure values and binary values that indicated whether there had been any potential exposure to Wells G and H. They do not discuss comparisons of exposure by year for the cases and controls. Based on their description of their exposure assessment method, they were most likely unable to refine their exposure assessment enough to assess the relationships with exposure that we were able to assess and identify.

The association Zelen and Lagakos identified may represent at least part of the relationship we identified between exposure during pregnancy and leukemia. How much of this is identified here however is uncertain. The exposure values they generated associated with the year of birth are not specific enough to identify exposures during pregnancy alone. Zelen and

Lagakos assigned values based on the year the individuals were born. This type of assessment would assign a mixture of exposure values from the year of conception and the year of birth. Children born early in the year (12 of the 21 cases were born on or before the 6th month of the calendar year allowing for a large amount of misclassification error) would be assigned an exposure value representing that year. More than one third of the cases would have been assigned an exposure score representing the calendar year after they were conceived. This means that the exposure during the first trimester of pregnancy (potentially the trimester for which the child is most sensitive to environmental exposures) would not have been considered in the assignment of an exposure score.

The observational analyses (summary statistics) used by Zelen and Lagakos do not consider short-term extremes of exposure which may have contributed to the association with illness particularly during specific developmental periods during pregnancy.

Concerns of information bias in their research have been suggested based on the fact that the researchers used local individuals not professionally trained, not blinded to the study hypotheses, and sometimes personally acquainted with the case families to conduct the telephone interviews used in data collection. These issues could certainly result in information bias specific to the medical information collected at interview. With regard to the exposure metric, however, residential history is not likely to be strongly biased no matter who collects the information. Other potential biases in the interview would do little to effect the exposure assessment as water exposure values are based specifically on residential history data and the Waldorf-Cleary model.

Plausibility of Results

According to the Wells G and H site assessment of February 21, 1989, in May of 1979 DEP (formerly DEQE) detected trichloroethylene, trans 1,2 dichloroethylene, chloroform, 1,1,1 trichloroethane, tetrachloroethylene, and trichlorotriflouro-ethane at levels up to 400 ug/liter in samples from Wells G and H. Benzene, a well documented human carcinogen, was not identified as a contaminant in the wells. All sampling information is based on a one time only sample of water from the wells and does not allow for a historical understanding of the concentrations of these compounds in the past or how the concentrations of contaminants may have changed over time.

The Agency for Toxic Substances and Disease Registry (ATSDR) health assessment for the Wells G and H site states that the hydrogeologic characteristics in the area of influence for Wells G and H is dynamic and therefore there could be a variety of factors that influence the primary direction from which the wells were to draw over time. Given this fact it would be difficult to predict historically the exact blend of contaminants at any given time.

Concerns have risen that potential benzene contamination at the nearby Industri-Plex National Priority List (NPL) hazardous waste site may have introduced benzene into the Wells G and H groundwater. An Agency for Toxic Substances and Disease Registry (ATSDR) preliminary health assessment concerning the adjacent Industri-Plex site indicates that any benzene which may have been present on the Industri-Plex site could not have impacted Wells G and H (Reference J).

The single compound found in highest concentration in the well water was trichloroethylene (TCE) found to be at a concentration of 267 ppb. The Environmental Protection Agency's (EPA) maximum contaminant level (MCL) for drinking water is 5 ppb. TCE is a common industrial solvent. Exposure to TCE has shown a variety of health effects in

animals and man. Much of the epidemiologic analysis that has been done to assess the effects of TCE on humans has occurred in the occupational environment. Results regarding cancer incidence have generally been negative even when large populations of workers who had been exposed to TCE for many years were followed over time (Tola, 1980). One recent study of over 14,000 military base workers who were exposed to TCE on the job for at least one year found no significant excess risk of cancer among workers of either sex (Spirtas, 1991).

Although occupational exposures among healthy adult workers have shown no association to cancer, it is difficult to extrapolate how this exposure may effect a general population that is likely to contain sensitive individuals. It is also unclear how a multi-chemical exposure which more likely occurred as a result of Wells G and H water consumption would have effected sensitive individuals, particularly since no information concerning which chemicals were present in the wells prior to 1979 is available.

Our major finding, the association of potential fetal exposure(s) to childhood leukemia risk suggests the necessity for further research to more clearly understand human sensitivity to multiple chemical exposures. Regular maternal ingestion of contaminated drinking water could lead to sustained blood levels of a mixture of contaminants whose fate in human tissues is unclear.

Confounding and Bias

The survey instrument was designed to collect information concerning possible risk factors which may have contributed to the incidence of childhood leukemia in Woburn. Analyses were conducted to address the role of these potential confounders. Elevated odds ratios as reported are those associations that remained after adjustment. These variables

therefore showed independent associations with leukemia incidence when effects of potential confounding variables were held statistically constant.

We were concerned with the difficulty in statistically controlling for a variety of potential confounders without decreasing the reliability of the statistics to a point of uninterpretability. In order to do so we reviewed and applied Tukey's work (1991) regarding the creation and application of composite covariates. We weighted the composite covariate based on beta values derived from the individual effects of each potential confounder on each study subject. In doing so we feel we have constructed composites which are fair in summarizing the original covariates without losing significant information which would have been available had independent covariates been used. The use of composite covariates did narrow the confidence intervals to some degree, although the specific magnitude of the point estimates should be interpreted with caution. Consistency in the direction of identified associations, the identification of a dose-response relationship and an apparent decrease in leukemia incidence after the removal of the exposure are important criteria in support of our conclusions.

This study was conducted in a community that had received national attention with regard to leukemia incidence. The study was conducted as a follow-up to previous work for which some case families had previously been interviewed. Certainly study subjects were not blinded to our purpose. Although the interviewer was professionally trained, he was also not blinded to the purpose of the study nor the case or control status of study subjects during interview.

There is concern then regarding biased responses among case parents. For example, case parents who may have believed the contaminated water was the cause of their child's illness would be more likely to respond positively to questions concerning water consumption than if

they were unaware of why they were being asked the question. Our method of exposure assessment, however, functions independently of parents' perceptions as it is based on residential history information and the Murphy water distribution model.

CONCLUSIONS AND RECOMMENDATIONS

The findings in this study suggests that the relative risk of developing childhood leukemia was greater for those children whose mothers were likely to have consumed water from Wells G and H during pregnancy than those who did not. We also observed that the risk of leukemia significantly increased as the amount of contaminated water from Wells G and H delivered to the households increased. In contrast, there appeared to be no association between the development of childhood leukemia and consumption of water from Wells G and H by the children prior to their diagnosis.

Conclusions regarding associations between exposures by trimester of pregnancy and leukemia incidence are limited by high correlation between trimesters with regard to exposure. The trend toward more elevated odds ratio values among later trimesters should be interpreted with caution. Further study in other populations is necessary to definitively address this trend and examine potential embryologic windows of increased vulnerability to leukemogens.

In general, the conclusions are based upon imprecise estimates of leukemia risk because of the small number of subjects. This imprecision indicates that the magnitude or strength of an effect is unclear. When statistical significance is not achieved, an estimate of risk that appears to be increased may in fact be due to the statistical variability inherent with estimates based on small numbers. However, considering these limitations, different approaches were taken in the analysis to assess the validity of an association between exposure to water from Wells G and H

and risk of leukemia. The results consistently were in the direction of an association between exposure and risk, although the magnitude of the association remains unclear. Our conclusions are based on our study's ability to generate a body of evidence which addresses criteria for causal inference including consistency in direction of associations identified, a dose-response relationship with exposure, and a decrease in risk after the removal of the pathway of exposure.

Because testing of the wells was very limited, a clear picture of the extent and nature of contamination, as well as the history of contamination is not known. The increased incidence of leukemia during well operation, the significant reduction of incidence after well closure, and the association between exposure to Wells G and H water during pregnancy and leukemia from this study, though, are observations that warrant further study in other populations similarly exposed.

In 1987, a group of researchers from the Massachusetts Institute of Technology (MIT) decided to study the Woburn area by taking environmental samples and using these data to reconstruct patterns of contamination which were likely to have occurred during the industrial history of Woburn. Researchers hope within the next few years to quantify the amounts of hazardous materials in the Woburn area, better understand their present health risk, and develop methods of eliminating chemicals which pose a risk to human health from the environment (MIT, 1994).

Fortunately, for a period of nearly eight years beginning in the middle of 1986, no new cases of childhood leukemia had been diagnosed in Woburn. A recent review of cancer registry information at one major medical institution in Boston revealed that between 1994 and the present, three new cases of childhood leukemia have been diagnosed among Woburn residents. The identification of these cases is not greater than would have been expected based upon

statewide leukemia rates in children. Since 1986, childhood leukemia incidence in Woburn has fallen below that which would normally be expected in a community with Woburn's population.

The MDPH, having established a statewide cancer registry in 1982, conducts continuous cancer surveillance for all Massachusetts communities including Woburn. This surveillance effort allows annual assessment of incidence for all cancers in Massachusetts providing the opportunity for early identification of increases in cancer incidence and the opportunity for an assessment of potential causes. Through use of the cancer registry, surveillance of childhood leukemia, as well as other types of cancer among Woburn residents will continue in order to determine whether the pattern of incidence changes.

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Tables

Table 1: Frequency of control replacements required for completion of matching scheme

	Cases	# of Replacements Required per Case
	7 (37%)	0
	7 (37%)	1
	3 (15%)	2
	2 (11%)	3
Total	19 (100%)	

Table 2: Distribution of Control Replacements According to Reason for Replacement

Reason	Number (%)	Total (%)
Refusal		11 (44%)
Simply not interested	7 (64%)	
Invasion of privacy	2 (18%)	
Family moving away	1 (9%)	
Their child's interview would provide no new information to the study	1 (9%)	
Not Woburn resident for entire etiologic period of case		6 (24%)
English not spoken adequately to complete interview		1 (4%)
Unable to locate		7 (28%)
Total		25 (100%)

Table 3: Number of cases and controls by parental availability

Parent at Interview	Case	Control
Both parents present at interview	12 (68%)	31 (84%)
Parents interviewed at different times	2 (11%)	2 (5%)
One parent completed both interviews, second parent not included in study	4 (21%)	4 (11%)
Total	19 (100%)	27 (11%)

Table 4: Distribution of cases by leukemia cell type

Cell Type	Total Cases (%)	Participating Cases (%)
Acute Lymphoytic Leukemia (ALL)	17 (82)	15 (79)
Acute Myelogenous Leukemia (AML)	3 (14)	3 (16)
Chronic Myelogenous Leukemia (CML)	1 (5)	1 (5)
Total	21 (100)	19 (100)

Table 5 : Distribution by age category at diagnosis

Years of Age at Diagnosis	Total Cases (%)	Participating Cases (%)
0 – 4	9 (43)	9 (47)
5 – 9	4 (19)	3 (16)
10-14	7 (33)	6 (32)
15 – 19	1 (5)	1 (5)
Total	21 (100%)	19 (100%)

Table 6: Study subject frequency by exposure status and cumulative exposure to water from Wells G & H by exposure time period

Exposure Time Period	Exposure Category	Cases N=19 # (%)	Controls N=37 # (%)
From 2 Years Before Conception to Case Diagnosis (full etiologic period)	Never Ever	3 (15.8) 16 (84.2)	13 (35.1) 24 (64.9)
During 2 Years Before Conception	Never Ever	11 (57.9) 8 (42.1)	25 (67.6) 12 (32.4)
During Pregnancy	Never Ever	9 (47.4) 10 (52.6)	25 67.6 12 (32.4)
From Birth to Diagnosis	Never Ever	7 (36.8) 12 (63.2)	16 (43.2) 21 (56.8)

Table 7: Average weekly water distribution score ranges of values for Wells G and H by case-control status and exposure time period

Status	Exposure Time Period	Ranges of Values
Cases	Before Conception	0.00-0.20
	During Pregnancy	0.00-0.23
	From Birth to Diagnosis	0.00-0.14
Controls	Before Conception	0.00-0.11
	During Pregnancy	0.00-0.10
	From Birth to Diagnosis	0.00-0.07

Table 8: Relationship between case-control status and cumulative exposure to water from Wells G & H by exposure time period.

Exposure Time Period	Exposure Category	Unadjusted Odds Ratio (O.R.)* O.R. (95% C.I.)	Adjusted Odds Ratios** O.R. (95% C.I.)
From 2 Years Before Conception to Case Diagnosis (full etiologic period)	Never Ever	1.00 1.99 (0.52, 7.71)	1.00 2.39 (0.54, 10.59)
During 2 Years Before Conception	Never Ever	1.00 1.77 (0.39, 8.00)	1.00 2.61 (0.47, 14.37)
During Pregnancy	Never Ever	1.00 5.70 (0.67, 48.25)	1.00 8.33 (0.73, 94.67)
From Birth to Diagnosis	Never Ever	1.00 1.36 (0.00, 5.38)	1.00 18 (0.28, 5.05)

*Odds Ratios as estimates of relative risk calculated using a conditional logistic regression model.

**Adjusted using a composite covariate. Adjusted to control for socioeconomic status, maternal smoking during pregnancy, maternal age at birth of child, and maternal alcohol consumption during pregnancy.

Table 9A: Relationship between case-control status and cumulative exposure to water from Wells G & H by exposure time period.

Exposure Time Period	**Exposure Category**	**Unadjusted Odds Ratios (O.R.)*** **O.R. (95% C.I.)**	**Adjusted Odds Ratios**** **O.R. (95% C.I.)**
First Trimester	Never	1.00	1.00
	Ever	2.29 (0.43, 12.23)	3.25 (0.47, 22.65)
Second Trimester	Never	1.00	1.00
	Ever	5.70 (0.66, 49.20)	7.54 (0.70, 80.77)
Third Trimester	Never	1.00	1.00
	Ever	7.03 (0.83, 59.53)	6.82 (0.77, 60.08)

*Odds ratios as estimates of relative risk calculated using a conditional logistic regression model.

**Adjusted using a composite covariate. Adjusted to control for socioeconomic status, maternal smoking during pregnancy, maternal age at birth of child, and maternal alcohol consumption during pregnancy.

Table 9B: Correlation* coefficients between exposure to water from Wells G and H and trimester of pregnancy.

Trimesters	**First**	**Second**	**Third**
First	1.00	0.76	0.67
Second	0.76	1.00	0.84
Third	0.67	0.84	1.00

*Coefficients calculated using the Pearson product moment correlation.

Table 10: Study subject frequency by exposure status and trichotomous exposure category* based on exposure to water from Wells G & H by exposure time period.

Exposure Time Period	**Exposure Category**	**Cases N=19 # %**	**Controls N=37 # %**
From 2 Years Before Conception to Case Diagnosis (full etiologic period)	Never Least Most	3 (15.8) 9 (47.4) 7 (36.8)	13 (35.1) 11 (29.8) 13 (35.1)
During 2 Years Before Conception	Never Least Most	11 (57.8) 4 (21.1) 4 (21.1)	25 (67.6) 6 (16.2) 6 (16.2)
From Birth to Diagnosis	Never Least Most	7 (36.8) 7 (26.8) 5 (26.4)	16 (43.2) 8 (24.4) 12 (32.4)
During Pregnancy	Never Least Most	9 (47.4) 3 (15.8) 7 (36.8)	25 (67.6) 8 (21.6) 4 (10.8)

*Exposure category cut points are based on no exposure as the lowest category and the two higher categories divided such that fifty percent of exposed subjects are in each exposed parameter.

Table 11: Relationship between case-control status and trichotomous exposure category* based on exposure to water from Wells G and H by exposure time period.

Exposure Time Period	**Exposure Category**	**Unadjusted Odds Ratios** O.R. (95% C.I.)**	**Adjusted *** Odds Ratios O.R. (95% C.I.)**
From 2 Years Before Conception to Case Diagnosis (full etiologic period)	Never	1.00	1.00
	Least	3.52 (0.78, 26.41)	5.0 (0.75, 33.50)
	Most	2.41 (0.45, 13.01)	3.56 (0.51, 24.78)
During 2 Years Before Conception	Never	1.00	1.00
	Least	1.82 (0.34, 9.64)	2.48 (0.42, 15.22)
	Most	1.68 (0.26, 11.04)	2.82 (0.30, 26.42)
From Birth to Diagnosis	Never	1.00	1.00
	Least	2.24 (0.41, 12.37)	1.82 (0.31, 10.84)
	Most	0.98 (0.20, 4.71)	0.90 (0.18, 4.56)
During Pregnancy	Never	1.00	1.00****
	Least	2.36 (0.20, 28.48)	3.53 (0.22, 58.14)
	Most	14.00 (0.98, 195.60)	14.30 (0.92, 224.52)

*Exposure category cut points are based on no exposure as the lowest category and the two higher categories divided such that fifty percent of exposed subjects are in each exposed parameter.

**Odds Ratios as estimates of relative risk calculated using a conditional logistic regression model.

***Adjusted using a composite covariate. Adjusted to control for socioeconomic status, maternal smoking during pregnancy, maternal age at birth of child and maternal alcohol consumption during pregnancy.

****Test for trend is significant (P=0.045)

Table 12: Comparison of odds ratio* adjustment using a single composite covariate versus a multiple covariate adjustment logistic regression.

Exposure Time Period	**Exposure Score**	**Adjusted Using a Composite Covariate** O.R. (95% C.I.)**	**Adjusted Using All Covariates*** O.R. (95% C.I.)**
From 2 Years Before Conception to Case Diagnosis (full etiologic period)	Never Ever	1.00 2.39 (0.54, 10.5)	1.00 2.48 (0.53, 11.64)
During 2 Years Before Conception	Never Ever	1.00 2.61 (0.47, 14.3)	1.00 2.77 (0.51, 14.96)
From Birth to Diagnosis	Never Ever	1.00 1.18 (0.28, 5.05)	1.00 1.27 (0.29, 5.52)
During Pregnancy	Never Ever	1.00 8.33 (0.73, 94.6)	1.00 13.20 (0.85, 205.20)

*Odds Ratios as estimates of relative risk calculated using a conditional logistic regression model.

**Adjusted using a composite covariate. Adjusted to control for socioeconomic status, maternal smoking during pregnancy, maternal age at birth of child, and maternal alcohol consumption during pregnancy.

***Controlling for socioeconomic status, maternal smoking during pregnancy, maternal age at birth of child, and maternal alcohol consumption, each covariate included as part of a single logistic regression model.

Table 13: Relationship between case-control status and exposure to water from Wells G and H during pregnancy for the total number for leukemias and by acute lymphocytic leukemias (ALL) only.

Leukemia Type	**Number of Cases**	**Odds Ratios 95% C.I.**
Total Leukemias* Among Study Participants	19	5.69 (0.66, 49.20)
Acute Lymphocytic Leukemia (ALL)	15	2.86 (0.30, 27.22)

*The total number of leukemias among study participants is composed of fifteen ALL cases, three ALL cases, and one CML case.

Table 14: Relative risk of leukemia in children of parents who worked in "High Risk" industry or occupation during the study period by sex of parent.

Parent	**Cases**	**Controls**	**Odds Ratio* O.R. (95% C.I.)**
Mothers			
High Risk Industry	5	12	0.79 (0.24, 2.57)
High Risk Occupation	5	12	0.71 (0.19, 2.82)
Father			
High Risk Industry	16	13	2.55 (0.78, 8.30)
High Risk Occupation	17	34	0.75 (0.13, 4.47)

*Odds ratios as estimates of relative risk calculated using a conditional logistic regression model.

Table 15: Distribution among industry groupings of maternal employment during the study period.

Industry Category	**Cases # (%)**	**Controls # (%)**
Agriculture, Forestry and Fisheries	0 (0.00)	0 (0.00)
Mining	0 (0.00)	0 (0.00)
Construction	0 (0.00)	0 (0.00)
Manufacturing (non-durable goods)	0 (0.00)	3 (7.1)
Manufacturing (durable goods)	4 (26.7)	8 (19.0)
Transportation, Communications and Other Public Utilities	2 (13.3)	2 (4.8)
Wholesale Trade (durable and non-durable goods)	0 (0.00)	0 (0.00)
Retail Trade	0 (0.00)	8 (19.0)
Finance, Insurance, and Real Estate	2 (13.3)	4 (9.5)
Business and Repair Service	1 (6.7)	2 (4.8)
Personal Services	0 (0.00)	2 (4.8)
Entertainment and Recreational Services	0 (0.00)	0 (0.00)
Professional and Related Services	6 (40.0)	12 (28.6)
Public Administration	0 (0.0)	1 (2.4)

Mothers may have been employed in more than one occupation in the same industry and/or may have worked in more than one industry during the study period.

Table 16: Distribution among industry groupings of paternal employment during the study period*.

Industry Category	**Cases # (%)**	**Controls # (%)**
Agriculture, Forestry and Fisheries	0 (0.00)	0 (0.00)
Mining	0 (0.00)	0 (0.00)
Construction	2 (6.9)	9 (18.0)
Manufacturing (non-durable goods)	3 (10.3)	7 (14.0)
Manufacturing (durable goods)	8 (27.7)	9 (18.0)
Transportation, Communications and Other Public Utilities	4 (13.9)	6 (12.0)
Wholesale Trade (durable goods)	1 (3.4)	1 (2.0)
Wholesale Trade (non-durable goods)	1 (3.4)	0 (0.0)
Retail Trade	5 (17.3)	6 (12.0)

Table 17: Results pf matched case-control analyses: Estimated risk of leukemia in children for industries in which ten or more parents reported employment during the study period by sex of parent.

Industry Category	**Cases**	**Controls**	**Odds Ratio (C.I.)**
Mothers			
Manufacturer (durable goods)	4	8	1.0 (0.29, 3.51)
Professional and Related Services	6	12	0.94 (0.30, 1.1)
Professional Services in Hospital	3	7	0.78 (0.19, 3.23)
Fathers			
Construction	2	9	0.38 (0.08, 1.88)
Manufacturing (non-durable goods)	3	7	0.84 (0.20, 3.46)
Manufacturing (durable goods)	8	9	1.93 (0.63, 4.72)
Transportation, Communications, and Other Public Utilities	4	6	1.27 (0.33, 4.96)
Retail Trade	5	6	1.67 (0.51, 5.40)

Table 18: Distribution among occupational groupings of maternal employment during the study period*.

Occupational Category	**Cases # (%)**	**Controls # (%)**
Managerial and Professional Specialty Occupations		
Executive, Administrative, and Managerial Occupation	2 (7.4)	1 (1.9)
Professional Specialty Occupations	0 (0.0)	0 (0.0)
Technical, Sales and Administrative Support Occupations		
Technicians and Related Support Occupations	2 (7.4)	1 (1.9)
Sales Occupations	0 (0.0)	0 (0.0)
Administrative Support Occupations	7 (25.9)	10 (18.9)
Service Occupations		
Private Household Occupations	0 (0.0)	0 (0.0)
Protective Service Occupations	0 (0.0)	0 (0.0)
Other Service Occupations	1 (3.7)	6 (11.3)
Farming, Forestry and Fishing Occupations		
Precision Production, Craft and Repair Occupations Mechanics and Repairers	0 (0.0)	0 (0.0)
Construction Trades	0 (0.0)	0 (0.0)
Extractive Operations	0 (0.0)	0 (0.0)
Precision Production Operations	0 (0.0)	2 (3.8)
Operators, Fabricators and Laborers		
Machine Operators, Assemblers and Inspectors	0 (0.0)	2 (3.8)
Transportation and Material Moving Operations	0 (0.0)	2 (3.8)
Handlers, Equipment Cleaners, Helpers and Laborers	0 (0.0)	1 (1.9)
Homemakers	15 (55.6)	28 (52.7)

*Mothers may have been employed in more than one occupation in the same industry and/or may have worked in more than one industry during the study period.

Table 19: Distribution among occupational groupings of paternal employment during the study period*.

Occupational Category	**Cases** **# %**	**Controls** **# %**
Managerial and Professional Specialty Occupations		
Executive, Administrative, and Managerial Occupation	3 (10.7)	7 (13.7)
Professional Specialty Occupations	4 (14.4)	7 (13.7)
Technical, Sales and Administrative Support Occupations		
Technicians and Related Support Occupations	2 (7.1)	6 (11.8)
Sales Occupations	3 (10.7)	6 (11.8)
Administrative Support Occupations	3 (10.7)	3 (5.9)
Service Occupations		
Private Household Occupations	0 (0.0)	0 (0.0)
Protective Service Occupations	3 (10.7)	0 (0.0)
Other Service Occupations	0 (0.0)	0 (0.0)
Farming, Forestry and Fishing Occupations	0 (0.0)	2 (3.9)
Precision Production, Craft and Repair Occupations Mechanics and Repairers	0 (0.0)	2 (3.9)
Construction Trades	3 (10.7)	6 (11.8)
Extractive Operations	0 (0.0)	0 (0.0)
Precision Production Operations	1 (3.7)	3 (5.9)
Operators, Fabricators and Laborers		
Machine Operators, Assemblers and Inspectors	2 (7.1)	3 (5.9)
Transportation and Material Moving Operations	2 (7.1)	3 (5.9)
Handlers, Equipment Cleaners, Helpers and Laborers	2 (7.1)	3 (5.9)

*Fathers may have been employed in more than one occupation in the same industry and/or may have worked in more than one industry during the study period.

Table 20: Results of matched case-control analyses: Estimated risk of leukemia in children for occupational categories in which ten or more parents reported employment during the study period by sex of parent.

Occupation Category	**Cases**	**Controls**	**Odds Ratio (C.I.)**
Mothers			
Technical, Sales and Administrative Support Occupations	9	11	0.95 (0.34, 4.80)
Clerical	7	10	1.40 (0.50, 3.97)
Homemaker	15	28	1,28 (0.31, 4.10)
Fathers			
Managerial and Professional Specialty Occupations	7	14	1.23 (0.41, 3.73)
Executive Adm. Prof. And Managerial Occupations	3	7	0.85 (0.20, 3.46)
Professional Specialty Occupations	4	7	1.18 (0.30, 4.63)
Technical Sales and Administrative Support Occupation	8	15	1.13 (0.34, 3.75)

Table 21: Relationship between case-control status and reported use of chemicals at work.

Exposure	**Mothers Cases N=19**	**Mothers Controls N=37**	**Fathers Cases N=19**	**Fathers Controls N=37**	**Odds Ratios* O.R. (95% C.I.)**
Coke Oven Emissions	0	0	0	4	
Lead	0	0	5	13	0.57 (0.16, 1.97)
Polyvinyl Chloride	0	0	2	8	0.43 (0.09, 2.03)
Chloroform	1	1	3	2	
Ionizing Radiation	0	1	1	6	
Pesticides	1	5	2	7	
Herbicides	1	1	0	5	
Carbon Tetrachloride	0	0	3	10	0.52 (0.40, 2.16)
Benzene	0	0	1	7	
Toluene	0	0	2	5	
Xylene	0	0	2	6	
Trichloroethylene	0	0	4	7	0.82 (0.24, 2.86)
Methylene Chloride	0	0	2	3	
Solvents	0	3	9	21	0.53 (0.46, 2.20)

Table 22: Relationship between case-control status and selected main effects.

Main Effect	**Exposure Status**	**Cases N=19**	**Controls N=37**	**Odds Ratios** O.R. (95% C.I.)**
Maternal Alcohol Consumption During Pregnancy	No Yes	9 10	22 15	1.00 1.50 (0.54, 4.20)
Breast-Fed Study Subject	No Yes	12 7	34 3	1.00 10.17 (1.22, 84.50)
Paternal Grandfather Diagnosed with Cancer	No Yes	11 8	29 8	1.00 2.01 (0.73, 5.58)
Father Worked in High Risk Industry	No Yes	6 13	27 16	1.00 2.55 (0.78, 8.30)
Public Water was Subject's Primary Beverage	No Yes	4 15	17 20	1.00 3.03 (0.82, 11.28)

*Effect reported if there were 10 or more positive responses at interview and odds ratio >=1.5.
**Odds ratio as estimates of relative risk calculated using a conditional logistic regression model.

Table 23: Maternal employment outside the home and its relation to case-control status by segment of the etiologic period.

Time Period **	**Cases**	**Controls**	**Odds Ratio* O.R. (C.I.)**
3 Months Before Conception	10	16	1.59 (0.47, 5.46)
During First Trimester	8	18	0.59 (0.42, 2.56)
During Second Trimester	6	17	0.45 (0.11, 1.86)
During Third Trimester	6	13	0.86 (0.23, 3.26)

*Odds ratios as estimates of relative risk calculated using a conditional logistic regression model.

**Mothers may have been employed in more than one time period.

Table 24: Distribution of all residences by four level wire configuration code and disease status.

Wire Code	**Cases # (%)**	**Controls # (%)**	**Totals # (%)**
VHCC	2 (10.6)	6 (11.1)	8 (11.0)
OHCC	2 (10.5)	12 (22.2)	14 (19.2)
OLCC	14 (73.7)	32 (59.3)	46 (63.0)
VLCC	1 (5.3)	4 (7.4)	5 (6.8)
Total	19 (100.0)	54 (100.0)	73 (100.0)

Table 25: Distribution of all stable residences by four level wire configuration code and disease status

Wire Code	**Cases # (%)**	**Controls # (%)**	**Total # (%)**
VHCC	1 (6.7)	3 (12.5)	4 (10.2)
OHCC	2 (13.3)	3 (12.5)	5 (12.8)
OLCC	12 (80.0)	16 (66.7)	28 (71.9)
VLCC	1 (0.0)	2 (8.3)	2 (5.1)
Total	15 (100.0)	24 (100.0)	39 (100.0)

Table 26: Odds ratios in relation to dichotomized wire code categories for stable residences.

Wire Code Categories	**Odds Ratio**	**95% Confidence Interval**
HCC* vs. LCC** (matched analysis)	2.20	(0.37, 13.11)

*HCC= (VHCC+OHCC)
**LCC= (OLCC+VLCC)