Case-control Study of Childhood Cancers in Dover Township (Ocean County), New Jersey

Volume II: Final Technical Report

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Division of Epidemiology, Environmental and Occupational Health
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INTRODUCTION

In the spring of 1995, the New Jersey Department of Health (now the New Jersey Department of Health and Senior Services or NJDHSS) was requested to evaluate childhood cancer incidence in the Toms River section of Dover Township by the federal Agency for Toxic Substances and Disease Registry (ATSDR). This request was precipitated by concerns raised by a health care practitioner from a nearby children's hospital who felt that a high number of children from the Toms River area were cancer patients at the treatment center.

To evaluate childhood cancer, the NJDHSS reviewed data from the New Jersey State Cancer Registry for the time period 1979 through 1991, a period representing all years of complete reporting at that time. Data on cancer in children (defined as under age 20 at time of diagnosis) were evaluated for Dover Township and an aggregate of four census tracts within Dover Township representing the Toms River section of the Township (see Figure 1). The designated Toms River area was established in consultation with the Ocean County Health Department.

In August 1995, NJDHSS completed its preliminary evaluation and concluded that childhood cancer incidence in Dover Township and the Toms River section was higher than expected for all malignant cancers combined, brain and central nervous system (CNS) cancers, and leukemia, and statistically significantly elevated for brain and CNS cancers in children under age five in Toms River (Berry, 1995).

In March 1996, residents of Dover Township met with state, federal, and local officials to voice concerns about childhood cancer in the community. In response, the NJDHSS and ATSDR developed a Public Health Response Plan (PHRP) detailing the course of action the agencies would follow to investigate childhood cancer and environmental concerns in Dover Township (NJDHSS and ATSDR, 1996). The PHRP was developed in coordination with the Citizens Action Committee on Childhood Cancer Cluster (CACCCC).

The PHRP included an updated childhood cancer incidence analysis through 1995, and evaluations of potential environmental exposure pathways in relation to two National Priorities List hazardous waste sites in Dover Township: Ciba-Geigy (NJDHSS and ATSDR, 2001a) and Reich Farm (NJDHSS and ATSDR, 2001b), as well as the Dover Township Municipal Landfill (NJDHSS and ATSDR, 2001c). In addition, the NJDHSS, ATSDR, and the New Jersey Department of Environmental Protection (NJDEP) conducted an extensive water quality evaluation of the United Water Toms River (UWTR) community water supply serving much of the township (NJDHSS, NJDEP, and ATSDR, 2001).

Appendix A and B (located in Volume IV: Final Report Appendices) provide a brief discussion of the occurrence and diversity of childhood cancer (Appendix A) and a review of the literature on potential risk factors for childhood cancer (Appendix B).

Childhood Cancer Incidence in Dover Township

As part of the PHRP, the NJDHSS expanded the cancer incidence analysis to 1995. All childhood (under 20 years of age) cancers combined and groupings of selected childhood cancer types were evaluated for Ocean County, Dover Township, and the Toms River section of the Township. Variations in the rates of childhood cancers over time for each study area were also evaluated.

The results of this expanded analysis, summarized in the *Childhood Cancer Incidence Health Consultation* (Berry and Haltmeier, 1997), confirmed that the overall childhood cancer incidence was elevated in Dover Township (Standardized Incidence Ratio [SIR] = 1.3, 95% Confidence Interval [CI] = 1.1-1.7) and the Toms River section of the Township (SIR = 1.7, 95% CI = 1.1-2.5). The elevations were specifically noted among female children under age five in Toms River for acute lymphocytic leukemia (SIR = 9.2, 95% CI = 2.5-23) and for brain and CNS cancers (SIR = 11.5, 95% CI = 2.3-34). Although case counts fluctuated from year to year, the time trend analysis provided some evidence that the rates in Dover Township tended to be higher than expected during the mid to late 1980s.

Environmental Exposure Pathways

Early in the course of evaluating potential routes of community exposure to contaminants in the environment (exposure pathways) outlined in the PHRP, testing of the community water supply revealed a previously undiscovered contaminant, styrene-acrylonitrile (SAN) trimer, in groundwater from several of the wells in the Parkway well field (NJDHSS, NJDEP, and ATSDR, 2001). This compound, which had been present in earlier water quality tests but unidentified, was one of the substances dumped at the Reich Farm Superfund site in 1971 (NJDHSS and ATSDR, 2001b). The Parkway well field has been a major source of potable water for the UWTR public water distribution system since the mid-1970s and is located about one mile south of the Reich Farm Superfund site.

Drums of chemical waste, numbering in the thousands, were illegally disposed at Reich Farm in 1971, leading to extensive contamination of local groundwater (NJDHSS and ATSDR, 2001b). The specific chemical composition of the groundwater contamination in the past was not well characterized, but organic compounds including trichloroethylene, tetrachloroethylene, and the SAN trimer have been found in the contamination plume. Private well contamination in the area of Reich Farm is documented as early as 1974. Contamination of the Parkway well field was documented in 1986. Although it is not known when Reich Farm contaminants first impacted the Parkway well field, estimates range from ten to fifteen years after dumping (Sykes, 1999). NJDHSS and ATSDR concluded that the Reich Farm Superfund site was a public health hazard due to past exposures (NJDHSS and ATSDR, 2001b).

Beginning in 1952, the Ciba-Geigy Corporation site (formerly Toms River Chemical Company), located in Dover Township, produced organic dyes and intermediate products, epoxy resins, and speciality chemicals (NJDHSS and ATSDR, 2001a). Operations at the facility tapered off in the late 1980s and ceased in the mid-1990s. Solid and liquid wastes from the manufacturing processes were disposed of in about 20 acres of the site's property, resulting in soil and groundwater

contamination. Between 1952 and 1966, treated wastewater was discharged directly into the Toms River. From 1966 to 1991, treated wastewater was discharged into the Atlantic Ocean by way of a ten-mile long pipeline across Dover Township (NJDHSS and ATSDR, 2001a).

Groundwater in the vicinity of the Ciba-Geigy site has been contaminated with a variety of volatile organic compounds, or VOCs (chlorobenzene, chloroform, dichlorobenzenes, trichlorobenzenes, methylene chloride, trichloropropane, trichloroethylene, and tetrachloroethylene), metals, and possibly other chemicals (NJDHSS and ATSDR, 2001a). Groundwater from private wells (used for irrigation) in the vicinity of Ciba-Geigy was found to be contaminated with VOCs in the mid-1980s. Groundwater from public water system supply wells at the Holly Street well field was documented to be contaminated with dyes, nitrobenzene, and possibly other compounds during the mid-1960s (NJDHSS and ATSDR, 2001a). Contaminated groundwater beneath the Ciba-Geigy site is currently being pumped out, treated, and re-injected into the aquifer.

Other potential exposure pathways from the Ciba-Geigy facility in the past include inhalation of contaminants released to the ambient air from on-site manufacturing and waste disposal activities (NJDHSS and ATSDR, 2001a). In 1986, off-site ambient air monitoring on the east bank of the Toms River detected VOCs (benzene, chlorobenzene, chloroform, tetrachloroethylene, trichloroethylene, and toluene) possibly related to the Ciba-Geigy site. Odor complaints were periodically received by the Dover Township Board of Health (and later the Ocean County Health Department) from residents east and south of the Ciba-Geigy property (NJDHSS and ATSDR, 2001a).

Based on the evaluations conducted as part of the Public Health Assessment process, NJDHSS and ATSDR concluded that the Ciba-Geigy Superfund site represented a public health hazard due to past exposures (NJDHSS and ATSDR, 2001a).

Groundwater pollution, particularly due to VOC contamination, has been

detected in some areas of Dover Township. Some of these areas were impacted with contaminants from the hazardous sites described above or from other pollutant sources. Households using private well water in areas with groundwater contamination could have been exposed through this pathway.

Residents in Dover Township identified additional sites of potential environmental contaminants that were of concern to the community. One of these sites, the Oyster Creek Nuclear Generating Station located ten miles south of Dover Township, began operation in December 1969 and was of concern due to the unique nature of its releases. Additionally, residents identified the Ciba-Geigy Superfund site, the Ciba-Geigy pipeline, the Reich Farm Superfund site, a section of the Toms River where treated wastewater had been discharged for 14 years by the Ciba-Geigy facility, the Dover Township Municipal Landfill, the Ocean County Landfill, and the Toms River Coal Gas site as potential pathways of exposure and sites of concern.

In a separate investigation, the Environmental and Occupational Health Sciences Institute (EOHSI) evaluated attic house-dust in Dover and non-Dover households for the presence of select chemical and radiological contaminants. While there was little difference detected between the Dover and non-Dover homes, it was noted that cesium 137 levels were higher in the attics of older (pre-1970) houses (EOHSI, 2001a). EOHSI concluded that the elevated cesium 137 levels in older houses were primarily the result of above-ground nuclear weapons testing and global fallout that occurred in the 1950s and 1960s.

Study Objectives

The overall purpose of this exploratory epidemiologic study was to identify possible disease risk factors that might explain the elevated rates of select childhood cancers, specifically leukemia and brain and central nervous system cancers, in Dover Township. This was accomplished by evaluating the magnitude of associations between these select cancer groups and various factors. While no single risk factor was the focus of the study, the study was designed to examine specific hypotheses

about certain environmental exposure pathways identified in the community. These primary hypotheses include: exposure to two public drinking water supply sources with documented contamination (Parkway and Holly Street well fields); exposure to contaminated private wells in Dover Township; and exposure to a major air pollution source (Ciba-Geigy) in Dover Township.

Study Design Overview

The Dover Township childhood cancer epidemiologic study was an exploratory investigation which consisted of two separate case-control components. A case-control study design compares children with cancer to children without cancer in order to assess the differences in histories of exposure to potential risk factors. A case-control study design was selected because it is the best method for studying rare diseases (Schlesselman, 1982). This study focuses on two age groups, children diagnosed before 20 years of age and children who were diagnosed before age five. These were the age groups in which the elevated rates of cancer were previously found for Dover Township.

The *Interview Study* focuses on children diagnosed with selected types of cancer (cases) while resident in Dover Township, and comparison (control) children matched on age, sex, and residence in Dover Township. Cases were identified through the New Jersey State Cancer Registry. Matched controls were identified primarily through public school records. The Interview Study collected information through structured questionnaire-based telephone interviews of parents of case and control children. Four controls were selected for each case in order to increase the study's power (Breslow and Day, 1980).

The *Birth Records Study* was designed to look at childhood cancer cases whose mothers lived in Dover Township at the time of the case's birth but who were diagnosed with cancer in either Dover Township or elsewhere. Cases in the Birth Records Study were identified through the New Jersey State Cancer Registry and cancer registries in other states, through record linkage to New Jersey Vital Statistics

and Registration. Control children in the Birth Records Study were identified from birth records. The Birth Records Study collected and analyzed information available only from birth certificates. Ten controls were selected for each case.

Environmental Factors

The following possible risk factors correspond to the environmental exposure pathways identified earlier and represent the study's primary hypotheses. Potential exposure to other environmental risk factors were also evaluated in order to address additional community concerns. In order to conduct the exposure assessments for the environmental variables, each study residence in Ocean County was assigned a latitude and longitude coordinate (geocode) using geographic information system (GIS) software, paper maps, and information provided during interviews or extracted from birth certificates. All geocoding was performed by staff blinded to the case or control status of each study address. The detailed methods for geocoding are found in Appendix C of Volume IV.

Household drinking water source exposure: Drinking water source exposure indices were developed for ten well field sources of the UWTR water distribution system and eleven areas in Dover Township with documented groundwater contamination. The ten well fields constitute all points of entry for water distributed by the UWTR system for the study period, 1962 to 1996. UWTR well field source exposure indices were developed using the output from computer model simulations conducted by ATSDR (ATSDR, 2001).

In the Interview Study, additional information available included the following: type of drinking water (public distribution system or private well) each residence received from one year prior to birth to the year of diagnosis; residential conversion from a private well to a public system during occupancy at each residence; primary water for cooking and drinking in each residence (household tap, bottled water or both); use of a water softening or other household water treatment system in each residence; and the number of drinks (glasses per day) with household tap water

consumed by the mother prior to the child's birth and by the child after birth. In the Birth Records Study, the source of water used in the home (public water or private well) was unknown and it was assumed the residence was on public water if the water distribution system was on the street of the residence during the year of the child's birth.

Drinking water indices developed for the study include:

C   exposure to private wells located in eleven regions of Dover Township with documented evidence of groundwater contamination,

C   exposure to public water from ten separate well fields in the UWTR distribution system,

C   exposure to the above water sources factoring in the amount of water consumption (Interview Study only), and

C   exposure to Parkway and Holly Street well fields, in the UWTR system, after making temporal adjustments regarding the possible periods of contamination of each well field.

The water source indices were developed by calculating the average percent of water delivered to a child's residence(s) from each water source as estimated by ATSDR computer modeling for the UWTR well fields. The detailed methods for the drinking water source assessment are found in Appendix D of Volume IV.

Exposure to air pollution from point sources: Point source air pollution exposure indices were developed using the output from computer model simulations conducted by EOHSI (EOHSI, 2001b). Monthly air pollution estimates from the Ciba-Geigy facility and the Oyster Creek Nuclear Generating Station were generated for each study residence located in Ocean County. Since emission data needed for the modeling was not available for the Ciba-Geigy facility, annual production information was used to modify the monthly modeling estimates in order to take into account the variability of the facility's operations over the study period. The air pollution indices were developed by calculating the average exposure to air pollution from both point source emitters.   The detailed methods for the point source air pollution assessment

are found in Appendix F of Volume IV.

Residential proximity to sites of concern: Seven sites were selected for an assessment of residential proximity during the study period. These sites include the Ciba-Geigy Superfund site; the Ciba-Geigy pipeline, and in particular the four locations of documented pipeline breaks which occurred; the section of the Toms River between the Manchester border and the Garden State Parkway; the Reich Farm Superfund site; the Dover Township Municipal Landfill; the Ocean County Landfill; and the former Toms River Coal Gas plant. Proximity to sites of concern indices were developed based on the proportion of study time that a child resided within one-half mile from that site. The detailed methods for the proximity to sites of concern assessment are found in Appendix G of Volume IV.

Birth residence year of construction: Information on the year of construction of the house where the parents resided at the time of the child's birth was collected from Dover Township municipal records for birth residences in the Birth Records Study. In the Interview Study, information on the year of construction of the birth address was not collected during the interview. In addition, birth residences of children in the Interview Study were in many municipal locations and information on year of construction was not generally available for all birth addresses. Consequently, evaluation of year of construction was only conducted for the Birth Records Study. Birth residences were categorized into older homes (built prior to 1970) and newer homes (build from 1970 onward).

Other Factors

The following factors were collected by questionnaire (Interview Study) and the from the birth certificate (Birth Records Study). These other factors were included because they are frequently evaluated in studies of childhood cancer and could be confounding variables to the environmental factors discussed above.

<u>Interview Study</u>

Parental occupation: Parental occupation was collected by questionnaire from one year prior to birth to the year of diagnosis. Each job was classified using the North American Industry Classification System (U.S. Department of Commerce, 1998) and the Standard Occupational Classification (U.S. Department of Commerce, 1980) coding schemes for descriptive purposes. In addition, an industrial hygienist's (IH) hazard rating of exposure was conducted for each of eight chemical/substance categories and nine job/activity categories. Appendix H, Volume IV, provides detail on the parental occupational assessment.

Demographic, pregnancy and birth characteristics: Information collected by questionnaire included: the proportion of the child's life spent in Dover Township; mother's age; parental education; mother's previous pregnancy losses and terminations; and child's birth weight and birth order.

Family medical history: Cancer history in the child's biological relatives (siblings, parents, and grandparents) and sibling history of inherited diseases or birth defects was collected by questionnaire.

Health, medical conditions and procedures: Questionnaire information included: diagnoses of specific infections, other illnesses, or complications during mother's pregnancy; maternal use of antibiotics and steroids during pregnancy and breast-feeding; birth defects of child; mother's exposure to dental x-rays and exposure to diagnostic x-rays by frequency and body area irradiated during pregnancy; child's specific infections and major illnesses from birth to the end of the relevant period; child's immunization history; and child's exposure to dental x-rays and exposure to diagnostic x-rays by frequency and body area irradiated.

Dietary factors: Usual intake of cured meats (hot dogs, lunch meat, bacon, ham or sausage), fresh fruit or vegetables, multivitamins and tap water by the mother during pregnancy and by the child from birth to the date of diagnosis were collected by questionnaire.

Exposure to tobacco smoke and alcohol: Information available from the questionnaire included: mother's smoking frequency (cigarettes per day) and duration

during pregnancy; total average smoking frequency by others in the household during pregnancy; child's exposure to smoking in the household from the child's birth to the date of diagnosis; and mother's alcohol consumption (weekly servings of wine, beer or mixed drinks) during pregnancy.

Household-related exposures: chemicals, animals and electromagnetic fields: Information collected by questionnaire included: mother's (during pregnancy) and child's (from birth to the date of diagnosis) exposure to household and garden chemicals (including pesticides and herbicides); mother's and child's use of electric blankets and heated water beds (household appliance electromagnetic fields); and the child's exposure to household pets, farm animals, and geese or ducks.

Birth Records Study

Demographic, pregnancy and birth characteristics: Information collected from the birth certificate included: parental age and education; child's birth weight and birth order; prenatal care utilization; complications of pregnancy; delivery method; and congenital malformations or other abnormal conditions of the newborn.

Exposure to tobacco smoke and alcohol: Limited information was available from the birth certificate about the mother's use of tobacco and alcohol products during pregnancy.

INTERVIEW STUDY

Interview Study Methods

Geographic Area of Study: The geographic area for the Interview Study is Dover Township, Ocean County, New Jersey. Cases and controls were required to have resided within Dover Township during a specified period of time at a designated point in life, as described below.

Case Definition: The Interview Study primarily focused on the types of cancers that were found to be elevated in Dover Township. A case was defined as a child: 1) diagnosed with leukemia or nervous system cancer; 2) under age 20 at the time of his or her diagnosis; 3) diagnosed between January 1, 1979 and December 31, 1996; and 4) a resident of Dover Township at the time of diagnosis.

Case Recruitment: Cases in the Interview Study were identified through the New Jersey State Cancer Registry (SCR), a statewide population-based cancer registry with virtually complete cancer ascertainment (estimated to be greater than 99% complete) for the study period. The SCR's ascertainment of incident cancer occurs through mandated reporting by oncologists, hematologists, pathologists, other physicians, hospitals, and laboratories. It is unlikely that children who developed cancer were not diagnosed or treated for their disease, due to the severity of their illnesses. Therefore, it is reasonable to conclude that all incident childhood cancers occurring in the Dover Township area in the study period were registered in the New Jersey SCR, and included in the Interview Study.

After case parents were located (see Search Methods section), parents of eligible cases were contacted by mail through a letter introducing the study and inviting participation, with follow-up telephone contact as necessary.   Once the appropriate informed consent was obtained, a structured telephone interview was scheduled and completed with the child's mother. Fathers were interviewed to provide their own occupational histories. Mothers were asked to provide paternal

occupational information only when fathers were not available. When mothers were not available for interview, the interview was completed with the child's father or guardian.

Control Definition: Four controls were selected for each case child and matched to the case. A control was defined as a child who was: 1) a resident of Dover Township during the month and year of the matched case's cancer diagnosis; 2) the same sex as the matched case, and 3) the same age ($\pm$ 1 year) as the matched case.

Control Recruitment: Public school records were used for the identification of potential controls. Based on the 1990 U.S. Census, 93.2% of the school-aged children (grades 1 through 12) in Dover Township attended public school. Controls were randomly selected from lists of all Dover Township children attending school within the Toms River School District in the same grade during the year the case was diagnosed. The name, address, date of birth, and grade level was abstracted from school records for potential controls. This information was examined to determine if the child met the age, sex, and residence matching criteria. Potential controls who did not meet the criteria were replaced by the next eligible selection.

For cases who were diagnosed before school age, controls were selected from among those children entering first grade six years after the birth year of the case, with the additional requirement that the control was also living in Dover Township in the month and year the case child was diagnosed. For two recently diagnosed case children who were still younger than school age by the end of 1996, controls were randomly selected from certificates of Dover Township births in the birth year of the case and also had to have been a resident of Dover Township at the time of the case's diagnosis.

After parents of eligible controls were located (see Search Methods section), contact and interviewing proceeded in the same way as noted above for the cases.

Search Methods: NJDHSS staff attempted to locate all case and control families based on information held in the New Jersey State Cancer Registry and the

Toms River School District records, supplemented by electronic address databases located on the Internet. For case and control families whose location could not be verified by NJDHSS, New Jersey State Library staff assisted in searching a national credit file and the New Jersey Public Record File. An ATSDR contractor with extensive locating experience was also used for difficult-to-locate families.

Data Collection: A questionnaire was developed to gather information on possible risk factors and confounding variables. Collected information included: identifying and demographic data; residential history of mother and child; parental educational and occupational histories; family medical history (including cancer); pregnancy history of mother (including medical and exposure information during pregnancy with child); and child's medical and environmental exposure history. Staff, with extensive experience in interviewing patients with cancer, field-tested the questionnaire prior to use and conducted all study interviews.

Relevant Time Period: A relevant time period for data collection, consisting of two time frames, was constructed for each case: 1) from one year prior to the birth of the child, up to the birth (prenatal period); and 2) from birth through the month of diagnosis with cancer (postnatal period). The same time frames were constructed for matched controls with the relevant time period beginning one year prior to their own birth, and ending in the month of diagnosis of their matched case.

Analytic Methods: The relative risk of childhood cancers was computed for each of the exposure assessment variables using a logistic model (Schlesselman, 1982). In matched case-control studies, conditional logistic regression is the most frequently used analytic approach. For binary outcome measures, the logistic regression model offers a more robust linear regression (Szklo and Nieto, 2000). Conditional logistic regression is similar to logistic regression except that parameters are estimated taking into account the pairing or matching of cases and controls with respect to the variables that determine the matching.

Univariate (unadjusted) exposure odds ratios (ORs) were computed for four cancer groups using matched analyses (conditional logistic regression). An exposure

odds ratio is the ratio of the likelihood of exposure among cases relative to the likelihood of exposure among controls (Last, 2001). If the OR is above 1.0, then cases were more likely to be exposed than controls. Conversely, if the OR is below 1.0, then cases were less likely to be exposed than controls. The cancer groups separately analyzed include: leukemia and nervous system cancers (all cases); leukemia; all nervous system cancers; and brain and central nervous system cancers. The study subjects were divided into two age groups within each of the four cancer groupings: children diagnosed prior to age 20, and children diagnosed prior to age five.

While the OR is the best estimate based on the data, it does not indicate the extent to which chance may have contributed to the point estimate (OR). Confidence intervals (95%) were computed to indicate the precision of the OR estimates. With 95% confidence, the true value of an OR for an exposure variable is contained within the interval (Last, 2001). The confidence interval simultaneously provides an idea of the magnitude of the effect and the random variability of the point estimate (Rothman and Greenland, 1998). Points near the center of the confidence interval are more compatible with the data than points further away from the center. For an OR to be considered statistically significant, the confidence interval does not include the value 1.0.

For the environmental factors, odds ratios were calculated for each of three time periods: total study time, prenatal, and postnatal. Certain other factors were only evaluated for the prenatal and postnatal time periods. Since it is known that exposures during different exposure time windows in human development may have different effects, prenatal and postnatal analyses were conducted in order to evaluate these two separate and distinct exposure windows.

The potential causal association of a risk factor with an outcome was evaluated using a combination of criteria, including: strength of the association (the magnitude of the OR), statistical significance, consistency of findings of multiple measures for an exposure, apparent dose response effect, and evidence of a completed exposure

pathway.

Participation rates were tabulated for eligible cases and potentially eligible controls. The reason for nonparticipation of potential study subjects was noted. The distribution characteristics of the environmental risk factors and the other risk factor groupings by case and control status were tabulated without respect to matching.

Statistical analyses included calculation of descriptive statistics and univariate (unadjusted) analyses designed to assess the relationship between exposure to individual risk factors and case-control status. Some exposure variables were collected as continuous measures (for example: birth weight, gestational age, and number of cigarettes smoked). These variables were categorized for analysis. For variables examined in other epidemiologic studies of childhood cancer, cut-points for categorization of variables were based on values commonly used in previously published scientific literature (for example: birth weight and maternal age). For other variables, cut-points were chosen based on the distribution of values among controls. Generally, attempts were made to establish tertiles of approximately equal numbers of controls, unless there were obvious natural breaks in the distribution which dictated other choices.

Conditional logistic regression odds ratios for matched sets were computed using the Stata 6 statistical software (StataCorp, 1999) for each level of categorized exposure variable.

Odds ratios (and their 95% confidence intervals) in risk factor groups were graphed for leukemia and for brain and central nervous system cancers diagnosed in all ages combined. Only those exposure factors with a minimum of two cases in the exposed or unexposed categories were graphed.

As a measure of the association between the environmental indices, correlation coefficients were generated and presented. Bivariate conditional logistic regression analyses were conducted to evaluate potential confounding between the environmental indices and other factors which displayed a significant association with case status. Because of the relatively small number of study subjects, multivariate

analyses could not be conducted in this study, and even some bivariate analyses could not be conducted.

Interview Study Results

A total of 42 children were identified by the New Jersey State Cancer Registry with a diagnosis of leukemia or nervous system cancer while residing in Dover Township during the period 1979 through 1996. After initial contact with the families, however, it was determined that two of these children resided in other municipalities at the time of their diagnosis, leaving a total of 40 children that met the study's case definition. All eligible case families consented to participate in the study (Table 1).

Table 2 presents the age of diagnosis and cancer type of the 40 eligible cases. Leukemia accounted for 22 of the cases (55%) and nervous system cancers accounted for remaining 18 cases (5 of which were sympathetic nervous system cancers or 13% overall, and 13 were brain and central nervous system cancers or 33% overall).

Out of 238 potential control families that NJDHSS attempted to recruit for the interview study, 40 children were determined to be ineligible as control subjects. Of the 198 remaining families, 159 were eventually interviewed (Table 1). Four matched controls were interviewed for all cases except one, for whom three controls were interviewed. The control participation rate was 80% (159/198). Of the 39 potentially eligible controls who were not interviewed, parent refusals (19) and no response after repeated contact attempts (12) were the primary reasons for not being interviewed. Seven potential control families could not be located and the parents of one potential control child were either deceased or severely disabled.

A total of 199 subject families (40 cases and 159 controls) were interviewed and constitute the entire interview case and control study populations. The overall study participation rate was 84%. Of the 159 controls interviewed, 132 (83%) of these were original controls (i.e., originally selected as one of the four controls per

case), while 27 were selected only after an original control refused to participate or could not be found. All four of those originally selected were interviewed for 18 of the cases; three of the initial controls were interviewed for 16 of the cases; and two of the initial controls were interviewed for six of the cases. None of the cases had less than two of the initially selected controls interviewed.

Characteristics of the study interviews are presented in Table 3. All but one of the interviews were conducted by telephone. Two NJDHSS interviewers conducted nearly all of the interviews with each doing half of the case families, and 57% and 42% of the control families, respectively. One control family interview was conducted by a third NJDHSS interviewer. Birth mothers were interviewed for the maternal section of the questionnaire in 95% of the case families and 93% of the control families. Case and control birth fathers were interviewed for the paternal section of the questionnaire 63% and 58% respectively, while case and control birth mothers were interviewed for the father's section 33% and 40% respectively. The informant's cooperation and the quality of information were judged by the interviewers in the quality assessment section of the questionnaire (Interview Remarks) to be similar regardless of case or control status, with 99% of the interviews rated as good/dependable or better.

Environmental Factors
Household Drinking Water Source Exposure

Private Well Assessment: Table 4 presents frequency information for cases and controls who ever lived in a household with a private well located in one of 11 regions in Dover Township with a history of groundwater contamination. As shown on Tables 4 and 5, only two of the 40 cases (5%) were found to have ever resided in any of the regions. Of the case children, one resided within the Breton Harbors region and one resided in the miscellaneous street segments region. A similarly small percentage of control children, four out of 159 (3%), were found to have ever resided in any of the regions. Three study children (1 case and 2 controls) could not

be assessed for residence in a groundwater region due to insufficiently precise information for at least one of the residences they lived in during the study period.

Table 5 presents odds ratios for private well use while ever residing in any of the 11 Dover Township groundwater regions. Exposure to private wells in contaminated regions did not appear to be associated with case status. Figure 2 presents graphed odds ratios for ever living in any of the 11 groundwater regions for leukemia. Though not statistically significant, the odds ratios for total time and postnatal time were both over 5.0. The prenatal leukemia odds ratio could not be calculated, but there were two cases (1 male and 1 female) and no controls with private well usage in any of the groundwater regions.

Public Water Source Assessment: Table 6 presents frequency information for ten public water well field sources serving case and control residences. The water source indices were derived by averaging the monthly computer modeled estimates over three time periods (prenatal, defined as the 9 months prior to the birth month; postnatal; and the total time period). Months when the child's residence was not hooked up to the public water system in Dover Township were assigned zero values for the ten public well fields. Since the public water distribution system had multiple points of entry (well fields), each residence could receive water from one or more public well field. Three exposure categories were formed: low (receiving less than 10% of their water from the specified public well field); medium (receiving 10% to 49.9% of their water from the specified public well field); and high (receiving 50% or more of their water from the specified public well field). These cut points were chosen to differentiate little or no residential exposure to a public well field from significant potential exposure (i.e., 50% or more of all water delivered to that residence). Other cut points were also examined and will be discussed.

As seen in Figure 3 and Table 6, two well fields (Holly Street and Parkway) supplied the largest percentage of drinking water to case and control homes. The Parkway well field supplied the greatest amount of water, with 65% of the case children and 69% of the control children supplied with 10% or more of their drinking

water from this source. Holly Street well field supplied 35% of the cases and 45% of the controls with 10% or more of their water from this source. A small number of case and control homes received medium to high amounts of water from four other well fields (Berkeley, Brookside, Indian Head and Route 70), while the remaining well fields (Anchorage, Silver Bay, South Toms River and Windsor) supplied a negligible amount of water to the case and control homes (ATSDR, 2001).

Tables 7a through 7d present odds ratios for the Brookside, Holly Street, Indian Head, Parkway and Route 70 well fields. Exposure to these five well fields did not appear to be associated with case status. Odds ratios for the remaining five well fields (Anchorage, Berkeley, Silver Bay, South Toms River, and Windsor) were calculated, but are not presented in this report, as the number of cases and controls in the medium and high exposure categories were generally too sparse to generate odds ratios. Exposures to the remaining well fields in which odds ratios could be calculated did not appear to be associated with case status.

Figures 4a and 4b present graphed odds ratios for the medium or high category for average percentage of water, from select well fields, for leukemia and for brain and central nervous system cancers during the prenatal and postnatal periods. The graphed odds ratios appear to be distributed close to 1.0.

Although not presented, two other approaches based on the control distribution were used to create and test alternate estimated exposure variables. The first approach was a tertile cut point. The second approach was a low (0%), medium (greater than 0% to 49.9%), and high (50+%) cut point distribution. Exposure categories calculated using these alternative cut points did not appear to be associated with case status, or display very different odds ratios from those calculated using the initial cut point approach. All water exposure analyses also used the tertile cut point approach. However, since the results of these analyses did not significantly differ from the principal method for the development of exposure categories, results of the water exposure indices will be presented for the principal method.

Odds ratios were also calculated separately for males and females and are

presented in Tables 8a through 8d for the Brookside, Holly Street, Indian Head, Parkway and Route 70 well fields. Exposure to these well fields did not appear to be associated with case status when evaluated separately by sex.

Because of documented groundwater contamination of the Parkway and Holly Street well fields, odds ratios were also calculated with temporal adjustments regarding the possible initial period of contamination of these well fields. Exposure indices developed using contaminant time windows will be referred to as time-specific in later discussions. Although the actual transit time of contaminants from Reich Farm to the Parkway well field is not known (NJDHSS, NJDEP, and ATSDR, 2001), an estimated time of ten years was assumed (Sykes, 1999). The time-specific Parkway well field variable discounted months prior to January 1982 and only included exposures after this point. For the Holly Street well field, historic contamination was known to exist in the mid-1960s, but there are no data documenting how long contamination may have persisted. By the mid-1970s very little water from contaminated wells of the Holly Street well field was being pumped into the water distribution system. Consequently, the Holly Street time-specific water source variable discounted months after December 1975. All discounted months were given a value of zero prior to calculation of the new time-specific indices. Conditional logistic regression odds ratios for the time-specific Parkway and Holly Street well field indices were calculated and are presented in Tables 9a through 9d. Time-specific well field exposure did not appear to be associated with case status.

In addition, odds ratios for the Parkway and Holly Street time-specific indices were calculated by sex (Tables 10a through 10d). Although none of the odds ratios were statistically significant, odds ratios were elevated for the high exposure category for time-specific Parkway well field water during the prenatal period in females with leukemia for all ages combined (OR=4.99; 95% CI=0.80, 31.2) and for females diagnosed with leukemia before age five (OR=3.23; 95% CI=0.52, 20.1). None of the odds ratios for the high postnatal time-specific Parkway well field exposures were elevated for females diagnosed with leukemia.

Because of the uncertainty when contaminated groundwater reached the Parkway well field, odds ratios were recalculated using alternate temporal adjustments regarding the year the well field became contaminated. The original time-specific Parkway well field variable assumed an exposure period of 1982 through 1996. Eight annual incremental adjustments were made to calculate alternate prenatal time-specific Parkway well field variables assuming a contaminant transit time of as little as six years (1978) to as long as 14 years (1986), four years earlier and later than the original estimated year the well field became contaminated. For the shortest estimated transit time, the alternate time-specific Parkway well field variable discounted exposures prior to January 1978 (exposure period: 1978-1996). Each succeeding alternate time-specific Parkway well field variable discounted exposures incrementally forward in time by one year (exposure periods: 1979-1996; 1980-1996; 1981-1996; 1983-1996; 1984-1996; 1985-1996; and 1986-1996). During the prenatal period, the odds ratios remained elevated for the high exposure categories for all of the alternate time-specific Parkway well field water variable for females, with the 1984-1996 exposure period displaying the highest odds ratio (OR=14.7; 95% CI=0.79, 274). Of note, female leukemia cases in the high prenatal Parkway well field exposure category were all born after 1983.

Because of the uncertainty of the length of contamination of the Holly Street well field, odds ratios were recalculated using an alternate temporal adjustment regarding the year the well field no longer was contaminated. The original time-specific Holly Street well field variable assumed an exposure period of 1962 through 1975. The alternate pre- and postnatal time-specific Holly Street well field variables assumed contamination through 1980, the last year that any of the older contaminated wells in the well field were documented to be in operation. The odds ratios for the alternate time-specific Holly Street well field exposure were unremarkable and similar to the original time-specific (1962-1975) Holly Street well field analysis.

Public Water Source/Consumption Assessment: As an alternative method of analyzing the water source indices, source/consumption indices were created by combining the water source categories with the categories for the average maternal water consumption during pregnancy and the average child's water consumption (see Volume IV, Appendix D), based on interview responses concerning the estimate of daily tap water consumption (glasses per day). Tables 11a through 11d present odds ratios by water source/consumption rating (none/low, medium, and high) for the Brookside, Holly Street, Indian Head, Parkway and Route 70 well fields.

The high Parkway well field prenatal water source/consumption category was significantly associated with leukemia and nervous system cancers for all ages combined (OR=2.45; 95% CI=1.03, 5.83) and for children diagnosed before age five (OR=4.19; 95% CI=1.17, 15.0). A significant inverse association was found for the medium Parkway well field postnatal source/consumption category with leukemia for all ages combined (OR=0.11; 95% CI=0.02, 0.58). Although not statistically significant, the odds ratio for high Parkway well field prenatal water source/consumption was elevated for all nervous system cancers (OR=5.02; 95% CI=0.88, 28.4). Figures 5a and 5b present graphed odds ratios of select water source/consumption indices for leukemia and for brain and central nervous system cancers.

Table 12a through 12d present odds ratios for well field source/consumption by sex. The high Parkway well field prenatal water source/consumption category was significantly associated with leukemia and nervous system cancers in females for all ages combined (OR=3.43; 95% CI=1.14, 10.4). Although not statistically significant, odds ratios for high Parkway well field prenatal water source/consumption was elevated for females with nervous system cancers in all ages combined (OR=11.29; 95% CI=0.99, 129) and brain and central nervous system cancers in all ages combined (OR=7.29; 95% CI=0.66, 80.8).   A significant inverse association was found for the medium Parkway well field postnatal water source/consumption for females with leukemia, all ages combined (OR=0.07; 95% CI=0.01, 0.73).

Time-specific Parkway and Holly Street well fields water source/consumption indices were recalculated with a ten year temporal adjustment regarding the possible period of contamination of these well fields and are presented in Tables 13a through 13d. Significant inverse associations were found for the medium time-specific Parkway well field postnatal water source/consumption category for all children (OR=0.33; 95% CI=0.11, 0.99) and for children diagnosed before age five (OR=0.18; 95% CI=0.03, 0.92) with leukemia and nervous system cancer. Although not statistically significant, the odds ratio for high Parkway well field prenatal water source/consumption category was elevated for leukemia and nervous system cancers combined in all ages combined (OR=3.02; 95% CI=0.99, 9.24).

In addition, time-specific Parkway and Holly Street water source/consumption odds ratios were calculated by sex (Tables 14a through 14d). The high Parkway well field prenatal water source/consumption category was significantly associated with leukemia and nervous system cancers in females for all ages combined (OR=5.16; 95% CI=1.20, 22.1) and with leukemia in females for all ages combined (OR=5.96; 95% CI=1.12, 31.7). A significant inverse association was found for the medium Parkway well field postnatal water source/consumption category with leukemia in females, all ages combined (OR=0.10; 95% CI=0.01, 0.96). Holly Street time-specific well field exposure did not appear to be associated with case status.

An alternative method was used to derive the time-specific Parkway well field water source/consumption indices and consisted of multiplying the average number of glasses of tap water consumed (for the mother prenatally and the child postnatally) and the average percentage of time-specific Parkway well field water delivered. The new time-specific Parkway well field water source/consumption odds ratio remained elevated (OR=4.28; 95% CI=0.97, 18.9) for the prenatal time period for leukemia in females. Data tables for the alternative method indices are not presented in this Report.

Figures 6a and 6b present the graphed odds ratios of all the Parkway well field indices for leukemia in females. A pattern in the elevated odds ratios can be seen

for the high category of Parkway well field prenatal water exposure (Figure 6a). While the addition of tap water consumption to the water source variable only modestly increased the odds ratio, the time-specific adjustment noticeably increased the odds ratios for both the unadjusted water source and the time-specific water source/consumption variables with the latter becoming statistically significant. The odds ratios for high Parkway well field postnatal categories (Figure 6b) were all below 1.0. Although not presented graphically, the prenatal and postnatal Parkway well field odds ratios for leukemia in males and for brain and central nervous system cancers in females and males were randomly distributed around 1.0.

Exposure to Air Pollution from Point Sources

Table 15 shows the mean frequencies of the estimated ambient exposures to two point source air pollution emitters, the Ciba-Geigy facility and the Oyster Creek Nuclear Generating Station, for all case and control children over the total study period. The cut points for the low, medium and high categories in Table 15 were determined using the 50th and 75th percentile values within the control population. The three categories of exposure for estimated ambient air emissions from Ciba-Geigy are: less than 1.00; 1.00 to 2.17; and greater than 2.17 relative air impact units.

The three categories of exposure for estimated ambient air emissions from the Oyster Creek are: less than 0.080; 0.080 to 0.27; and greater than 0.27 femtoCuries per cubic meter (fCi/m^3). It is important to note that all of the estimated Oyster Creek ambient exposures (to iodine[131]) were far below the limit of detection of 70 fCi/m^3. A lifetime cancer risk to the exposure levels estimated by the computer modeling is extremely low, on the order of about one in a billion. Details concerning the model and construction of these indices are found in Appendix F, in Volume IV.

As shown in Table 15 for the total study time period, both the medium and high exposure categories for the average exposure to Ciba-Geigy ambient air emissions contained 30% of the case children and 25% of the control children.

Odds ratios for the average estimated ambient air emissions were calculated and shown in Tables 16a through 16d. Exposure to medium or high Ciba-Geigy ambient air emission categories did not appear to be associated with case status. Figures 7a and 7b present the graphed Ciba-Geigy ambient air odds ratios for the leukemia and for brain and central nervous system cancers.

As shown in Table 15 for the total study period, average exposure to ambient air emissions from Oyster Creek was estimated to be in the medium exposure category for 28% of the case children and 24% of the control children. Twenty percent of the case children and 25% of the control children were found to be in the high exposure Oyster Creek category.

As shown in Tables 16a through 16d, average estimated ambient exposure for Oyster Creek ambient air emissions did not appear to be associated with case status. Odds ratios for exposure to ambient air emissions from Oyster Creek for leukemia and for brain and central nervous system cancers are presented graphically in Figures 8a and 8b, respectively.

Odds ratios were also calculated separately for males and females (Tables 17a through 17d). The medium prenatal Ciba-Geigy exposure category was significantly associated with leukemia in females for all ages combined (OR=6.42; 95% CI=1.09, 37.8). Although not significantly associated, the odds ratios for the medium (OR=5.21; 95% CI=0.48, 56.5) and high (OR=18.9; 95% CI=0.90, 397) Ciba-Geigy exposure categories were elevated for leukemia in female children diagnosed prior to age five. Five of seven of the female leukemia cases under age five were in the medium or high Ciba-Geigy exposure categories while only nine of 27 controls were in those categories. When the medium and high Ciba-Geigy exposure categories were collapsed into a single exposure category, the new odds ratio for leukemia in females diagnosed prior to age five was elevated (OR=7.46; 95% CI=0.78, 71.3) relative to the low exposed group.

The odds ratio for the postnatal high exposure category was also elevated for Ciba-Geigy ambient air (OR=5.5, 95% CI=0.3, 122) for females diagnosed with

leukemia prior to age five.

Other Environmental Factors

Residential Proximity to Sites of Concern: Table 18 presents the number of case and control children who ever lived within one-half mile of each site of concern, along with the number who lived for more than 50% of their total study time within one-half mile of a site. With the exception of the Ciba-Geigy pipeline and Ciba-Geigy plant, few children ever lived within one-half mile of any of the sites of concern. Fourteen cases (35%) and 38 controls (24%) ever lived within one-half mile of the Ciba-Geigy pipeline. Five cases (13%) and 14 controls (9%) ever lived within one-half mile of a pipeline break after the break occurred. Five cases (13%) and 12 controls (8%) ever lived within one-half mile of the Ciba-Geigy pipeline. No cases and few controls ever lived within one-half mile of three of the sites of concern (Reich Farm, the Dover Township Municipal Landfill, and the Ocean County Landfill).

Tables 19a through 19d present odds ratios for having ever lived in proximity to a site of concern. Ever living within one-half mile of the Ciba-Geigy pipeline was found to be significantly associated with leukemia during the total time period for all ages combined (OR=2.63; 95% CI=1.03, 6.67) and for children diagnosed prior to age five (OR=7.09; CI=1.32, 38.2). In children diagnosed with leukemia prior to age five, odds ratios for the prenatal (OR=5.67; CI=0.95, 34.0) and postnatal (OR=5.53; CI=0.95, 32.2) time periods were elevated. Ever having lived within one-half mile from a pipeline break after the break occurred did not appear to be associated with leukemia.

Odds ratios for the proximity to sites of concern and childhood leukemia and for brain and central nervous system cancer are presented graphically in Figures 9a through 9c.

Tables 20a through 20d present odds ratios for having ever lived in proximity to a site of concern by sex for sites of concern with sufficient numbers of cases and controls to calculate odds ratios. Ever living within one-half mile of the Ciba-Geigy

pipeline was found to be significantly associated with leukemia and nervous system cancers combined during the total time period for all females combined (OR=3.62; 95% CI=1.34, 9.76) and for female children diagnosed prior to age five (OR=4.39; CI=1.16, 16.6). Ever living within one-half mile of the Ciba-Geigy pipeline was found to be significantly associated with leukemia and nervous system cancers combined during the postnatal time period for all females combined (OR=3.20; 95% CI=1.16, 8.84). Ever living within one-half mile of any of the Ciba-Geigy pipeline breaks was found to be significantly associated with leukemia and nervous system cancers combined during the total time period for all females combined (OR=3.33; 95% CI=1.02, 10.9) and the postnatal time period (OR=3.33; 95% CI=1.02, 10.9).

For all females with leukemia, ever living within one-half mile of the Ciba-Geigy pipeline was found to be significantly associated during the total time period (OR=6.97; 95% CI=1.83, 26.5), the prenatal time period (OR=5.12; CI=1.14, 22.9), and the postnatal time period (OR=6.00; CI=1.54, 23.4). For females diagnosed prior to age five with leukemia, ever living within one-half mile of the Ciba-Geigy pipeline was found to be significantly associated during the total time period (OR=16.9; 95% CI=1.94, 146), the prenatal time period (OR=11.2; CI=1.16, 108), and the postnatal time period (OR=13.7; CI=1.51, 125).

Ever living within one-half mile of any of the Ciba-Geigy pipeline breaks was found to be significantly associated with leukemia in all females during the total time period (OR=4.00; 95% CI=1.00, 16.0) and the postnatal time period (OR=4.00; CI=1.00, 16.0).

Environmental Index Correlations

Each of the environmental risk factor indices for the primary study hypotheses, exposure to time-specific Parkway well field water, exposure to time-specific Holly Street well field water, and exposure to Ciba-Geigy ambient air emissions, were evaluated for their correlation with the other environmental indices: other public well field waters, proximity to all sites of concern, and Oyster Creek ambient air

emissions. The statistically significant correlations coefficients (p<.01) for the total time period are presented in Table 21. The time-specific Parkway well field index was statistically inversely correlated with the time-specific Holly Street well field index (r=-0.25) and the Oyster Creek ambient air index (r=-0.37) and statistically correlated with the proximity to Ciba-Geigy pipeline index (r=0.30) and the proximity to Ciba-Geigy pipeline breaks index (r=0.23).

The time-specific Holly Street well field index was statistically correlated with the Ciba-Geigy ambient air index (r=0.36), the Oyster Creek ambient air index (r=0.51), the Indian Head well field index (r=0.22), the proximity to Ciba-Geigy index (r=0.26), and the proximity to the section of the Toms River index (r=-0.31).

In addition to its correlation to the time-specific Holly Street well field index mentioned above, the Ciba-Geigy ambient air index was also statistically correlated with the Oyster Creek ambient air index (r=0.21), the Indian Head well field index (r=0.56), the Route 70 well field index (r=0.47), the proximity to Ciba-Geigy site index (r=0.81), and proximity to the section of the Toms River index (r=0.68).

The correlation coefficients among prenatal exposure indices were also calculated and followed a similar pattern. Many of the environmental risk factor indices in the Interview Study were significantly correlated with each other.

Other Factors

Parental Occupation

Complete or partial occupational exposure data for one or more parents were obtained from the interview questionnaire for all 199 study participants. As shown in Table 22, occupational exposure information for the birth parents were available for greater than 97% of all study participants. Occupational exposure data for 392 birth parents were combined with data for 17 adoptive parents, step-parents, or custodial parents to create maternal and paternal occupational composites for each study participant. Data were absent for one maternal and one paternal occupational composite for different study subjects. The composite parents will hereafter be

referred to as the "mother" and "father".

A total of 1,272 jobs or hobbies were reported. As shown in Table 22, the average number of jobs held during the relevant time interval was higher for mothers (3.8 among cases and 3.3 among controls), than fathers (2.8 among cases and 2.7 among controls). The maximum number of jobs reported was 12 among fathers, and 11 among mothers.

As shown in Table 23, the most frequently reported Standard Occupational Classification (SOC) category among mothers included homemaker, unemployed, disabled or retired, with 82% of case mothers and 90% of control mothers reporting at least one interval in this category. Other frequently reported occupational categories among case and control mothers were: marketing and sales occupations (18% vs. 20%); administrative support occupations, including clerical (40% vs.36%); and service occupations (18% vs. 20%). Among case and control fathers, the most frequently reported SOC category was marketing and sales occupations (20% vs. 23%). Other frequently reported occupational categories among case and control fathers were: executive, administrative and managerial occupations (18% vs. 18%); service occupations (10% vs. 18%); mechanics and repairers (23% vs. 14%); and construction and extractive (drilling, blasting, and mining) occupations (18% vs. 16%).

Homemaking, although not a category in the North American Industry Classification System (NAICS), was the most frequently reported activity for mothers with 85% of case mothers and 90% of control mothers reporting at least one interval of being a homemaker, unemployed, disabled or retired (Table 24). The most frequently reported NAICS categories among case and control mothers were: retail trade (20% vs. 24%); health care and social assistance (28% vs.18%); finance and insurance (13% vs. 9%); educational services (15% vs.14%); and accommodation and food services (15% vs. 13%). Among case and control fathers, the most frequently reported industrial category was construction (23% vs. 20%), followed by manufacturing (18% vs.15%); retail trade (18% vs. 23%); and public administration (15% vs. 19%).

Frequencies of maternal and paternal exposure to selected job activities and chemicals, as rated by an industrial hygienist (IH) blinded to the case or control status of study participants, are shown in Table 25. Few mothers reported any occupations or hobbies that would lead to exposure to the listed substances or activities. Substances of interest most frequently used by case and control mothers include: plastics and resins (8% vs. 13%); and ionizing and low frequency radiation (28% vs. 16%). Job activities of particular interest that were the most frequent among case and control mothers include: painting, printing, dye coloring, and graphics (13% vs. 15%); electrical and electronics (28% vs. 17%); and medical professions (8% vs. 13%).

As shown in Table 25, fathers appear to have more occupational experiences with the substances and activities of interest. Case and control paternal occupational exposures were most frequent for the following substances: solvents, dry cleaning agents and degreasers (25% vs. 21%); paints and thinners (18% vs. 14%); petroleum products (40% vs. 30%); plastics and resins (33% vs. 21%); metals (20% vs. 19%); and ionizing and low frequency radiation (25% vs. 24%). Case and control paternal job activities occurring most frequently were: painting, printing, dye coloring and graphics (13% vs. 19%); electrical and electronics work (30% vs. 25%); metal work (15% vs. 14%); and motor vehicle work (20% vs. 25%).

Tables 26a through 26d present IH rating odds ratios for 17 maternal and 17 paternal occupational activity/substance categories. Two maternal IH rated job activity/substance categories were statistically associated with case status. The category "ever did electrical or electronics work" was significantly associated with brain and central nervous system cancers during the postnatal period (OR=12.4, 95% CI=1.37, 111) and the total study period (OR=10.3, 95% CI=1.14, 93.4); and with leukemia and nervous system cancers during the postnatal period (OR=2.99, 95% CI=1.19, 7.49). The category "ever exposed to radiation (ionizing or low frequency)" was significantly associated with leukemia and nervous system cancers during the postnatal period (OR=3.19, 95% CI=1.22, 8.30). Figures 10a

through 10d present selected graphed maternal odds ratios for leukemia and for brain and central nervous system cancers.

Four paternal IH rated job activity/substance categories (shown in Tables 26a through 26d) were found to be statistically significantly associated with case status. The category "ever exposed to dyes or pigments" was significantly associated with leukemia and nervous system cancers during the total study period (OR=12.0, 95% CI=1.25, 115), the prenatal period (OR=12.0, 95% CI=1.25, 115), and the postnatal period (OR=12.0, 95% CI=1.25, 115). The category "ever worked in chemical manufacturing" was significantly associated with leukemia and nervous system cancers during the total study period (OR=5.33, 95% CI=1.19, 23.8), the prenatal period (OR=16.0, 95% CI=1.79, 143), and the postnatal period (OR=5.33, 95% CI=1.19, 23.8). The category "ever did electrical or electronics work" was significantly associated with leukemia during the postnatal period (OR=3.04, 95% CI=1.10, 8.37). The category "ever exposed to petroleum products" was significantly associated with leukemia during the prenatal period (OR=2.83, 95% CI=1.03, 7.81). Figures 10e through 10h present the graphed paternal odds ratios for leukemia and for brain and central nervous system cancers.

Demographic, Pregnancy and Birth Characteristics

Table 27 presents demographic, pregnancy, and birth characteristics of the study population. There were an equal number, 20 each, of male and female cases. Virtually the entire study population was white and non-Hispanic. The period 1980-84 contained the most case births, 14 or 35% of all cases combined in the Interview Study, and the period 1987-90 contained the most case diagnoses, 12 or 30%.

In general, the frequency of most of the demographic, pregnancy, and birth characteristics did not differ by case status. More case mothers resided in Dover Township during part or all of their pregnancy with their offspring (63%) compared with control mothers (52%). Cases (78%) attended day care, camps, and/or schools more frequently than controls (68%). Case birth mothers tended to have slightly

more education (25% had at least a college degree) than control birth mothers (18% had at least a college degree), whereas case birth fathers had slightly less education (23% had at least a college degree) than control birth fathers (32% had at least a college degree). Average birth weight for cases (3,499 grams) was slightly higher than for controls (3,352 grams).

Tables 28a through 28d present the odds ratios for demographic, pregnancy, and birth characteristics. Odds ratios for mother's and father's educational levels were mixed, ranging from 0 to 5.89. A significant inverse association was found for the high paternal education (some college or higher) with leukemia in all ages combined (OR=0.20; 95% CI=0.05, 0.76), while high maternal education (some college or higher) was significantly associated with nervous system cancers in children diagnosed before age five (OR=5.89; 95% CI=1.07, 32.4). Children in larger families (mothers with four or more total live births) had a significantly elevated odds ratio for leukemia and nervous system cancers combined for the younger age group (OR=3.63; 95% CI=1.08, 12.2), which appeared to be driven by the incidence in children diagnosed with leukemia (OR=3.94; 95% CI=0.85, 18.2).

Figures 11a and 11b present the graphed odds ratios for demographic, pregnancy, and birth characteristics by leukemia in all ages and brain and central nervous system cancers. Odds ratios for exposure variables evaluated in this potential risk factor group display were above and below 1.0.

  Family Medical History

Table 29 presents self reported information on family medical history of cancer and inherited health problems or birth defects. The frequencies of reported inherited problems or birth defects in study children or their siblings were similar for both case and control groups. The self reported responses were reviewed by staff of the New Jersey Birth Defects Registry to provide guidance on conditions that should be considered a likely birth defect. Both case and control groups were similar in the frequency of likely birth defects for study children and their siblings.

Family history of any type of cancer and brain cancer was similar for cases and controls. Family history of leukemia was higher for case families (5%) than control families (1%). History of any type of cancer in grandparents was similar for case and control groups, but history of any type of cancer in parents was higher in case families (10%) than control families (5%). No cancer was reported in any study child's siblings.

Tables 30a through 30d present the odds ratios for family medical history. Family history of cancer, inherited health problems, or birth defects did not appear to be associated with cancer incidence. Although not statistically significant, the odds ratio for a history of any type of cancer in parents was elevated among children with nervous system cancers (OR=7.29; 95% CI=0.66, 80.8) based on few positive responses. This appears to be driven by the sympathetic nervous system cases since the odds ratio for a history of any type of cancer was much lower in the parents of children with brain and central nervous system cancers (OR=1.26).

Figures 12a and 12b present the graphed odds ratios for family medical history variables for leukemia and for brain and central nervous system cancers. Since many exposure variables evaluated in this potential risk factor group had a relatively low positive response rate, few exposure factors could be graphically depicted, especially for brain and central nervous system cancers. Those factors presented appear to be distributed around 1.0.

Health, Medical Conditions and Medical Procedures

Table 31 presents information on health, medical conditions, and medical procedures as reported by parents. No mothers reported having measles, rubella, chickenpox, or cytomegalovirus during pregnancy with the study child. The frequency of most prenatal medical conditions and medical procedures was similar for cases and controls. Maternal exposure to dental x-rays during pregnancy was lower among cases (23%) than controls (29%), while diagnostic x-rays or radiation therapy was higher among case mothers (13%) than control mothers (6%). Of the 14 mothers

who had diagnostic x-rays while pregnant, 13 mothers (5 cases and 8 controls) had a single x-ray and one mother (1 control) had two x-rays.

The frequencies of most postnatal medical conditions and medical procedures were similar for cases and controls. Cases had higher rates of other (non-cancer) major illnesses (40%) than controls (27%). Exposure to dental x-rays was lower in cases (48%) than controls (53%), while diagnostic x-rays or radiation therapy was higher in cases (38%) than controls (26%). Of the 56 children who received a diagnostic x-ray or radiation therapy, 91% (14 cases and 37 controls) had no more than two exposures and no child had more than four exposures. The interview responses indicated that the reported diagnostic x-rays or radiation therapy exposures were diagnostic x-rays and not radiation therapy, based on the infrequency of exposure and the lack of illnesses reported that are treated with radiation. Consequently, the exposure factor diagnostic x-rays or radiation therapy will be referred to as diagnostic x-rays.

Tables 32a through 32d present the odds ratios for health, medical conditions, and medical procedures. Odds ratios for antibiotic use for ten days or longer by a child was elevated for all age and cancer groupings and significantly elevated for leukemia and nervous system cancers, all children and all ages combined, (OR=2.37; 95% CI=1.02, 5.54) and all children diagnosed prior to age five (OR=4.35; 95% CI=1.17, 16.1).

Exposure of the child to diagnostic x-rays was significantly associated with leukemia and nervous system cancers for all children diagnosed prior to age five (OR=4.67; 95% CI=1.49, 14.6). This elevation appears to be driven by the elevated odds ratio for diagnostic x-rays and nervous system cancers in children diagnosed prior to age five (OR=6.64; 95% CI=1.19, 36.9). Although receiving diagnostic x-rays more than once did not appear to be associated with any cancer grouping, a single postnatal diagnostic x-ray was significantly associated with leukemia and nervous system cancers for all children diagnosed prior to age five (OR=5.13; 95% CI=1.40, 18.8) and with leukemia for all children diagnosed prior

to age five (OR=9.43; 95% CI=1.02, 87.4).

In order to evaluate the possible differences in exposure to x-ray intensity over time, diagnostic x-rays were stratified by those occurring prior to 1985 and those occurring from 1985 onward. The pre-1985 exposure of the child to diagnostic x-rays were significantly associated with leukemia and nervous system cancers for all children diagnosed prior to age five (OR=5.93; 95% CI=1.02, 34.6). From 1985 onward, the odds ratio for exposure of the child to diagnostic x-rays remained elevated, but not significant for leukemia and nervous system cancers.

Because of concerns that diagnostic x-rays could be part of the medical evaluation of a case prior to his or her diagnosis, a child's exposure to diagnostic x-rays was also evaluated by eliminating from the analysis those x-rays received within one year of the end of the relevant time period (i.e., the date of cancer diagnosis). The resulting odds ratios were substantially lower and none were statistically significant. The odds ratio for postnatal diagnostic x-rays for children diagnosed prior to age five with leukemia and nervous system cancers was reduced from 4.67 to 1.36 (95% CI=0.28, 6.7.) and for nervous system cancers in children diagnosed prior to age five it was reduced from 6.64 to 0. The odds ratio for a single postnatal diagnostic x-ray for children diagnosed prior to age five with leukemia and nervous system cancers was reduced from 5.13 to 1.75 (95% CI=0.34, 9.05) and for leukemia in all children diagnosed prior to age five, it was reduced from 9.43 to 2.24 (95% CI=0.39, 13.0).

Figures 13a through 13d present the graphed odds ratios for health, medical conditions, and medical procedures exposure variables by leukemia and for brain and central nervous system cancers. The factors presented appear to be randomly distributed around 1.0.

Dietary Factors

Table 33 presents prenatal and postnatal dietary information. Mother's cured meat consumption during pregnancy is defined as: consumption of either bacon,

ham, or sausage; hot dogs; or lunch meat. In the following discussion, the term weekly refers to consumption of a specific dietary factor one or more times per week.

During pregnancy, case mothers reported lower rates than control mothers for a number of dietary exposures, including: any hot dog consumption (68% vs. 79%); weekly hot dog consumption (8% vs. 21%); weekly consumption of bacon, ham, or sausage (13% vs. 40%); any consumption of lunch meats (80% vs. 86%); weekly consumption of lunch meats (45% v. 64%); weekly cured meat consumption (55% vs. 76%); and multivitamin supplementation for five days or more (63% vs. 81%). Postnatal dietary information were generally similar for cases and controls.

Tables 34a through 34d present the odds ratios for dietary factors. The dietary factors risk group displayed wide fluctuations in odds ratio magnitudes. Generally, prenatal dietary variables tended to display odds ratios below 1.0 while the postnatal dietary variable odds ratios tended to be more inconsistent.

For all study children combined, a number of significant inverse associations were found for leukemia and nervous system cancers and include: mother's weekly consumption of lunch meat during pregnancy (OR=0.44; 95% CI=0.22, 0.91); mother's weekly consumption of bacon, ham, or sausage during pregnancy (OR=0.21; 95% CI=0.08, 0.57); mother's weekly consumption of cured meat during pregnancy (OR=0.34; 95% CI=0.16, 0.74); and mother's use of multivitamin supplements for five or more days during pregnancy (OR=0.38; 95% CI=0.16, 0.89). In all children diagnosed under age five, a number of significant inverse associations were found for leukemia and nervous system cancers and include: mother's use of multivitamin supplements for five or more days during pregnancy (OR=0.20; 95% CI=0.05, 0.86), mother's weekly dietary consumption of lunch meat during pregnancy (OR=0.30; 95% CI=0.10, 0.93) and mother's weekly consumption of cured meat during pregnancy (OR=0.24; 95% CI=0.07, 0.85).

Significant inverse associations were found for leukemia, all ages combined, and include: mother's consumption of any hot dogs during pregnancy (OR=0.30; 95% CI=0.10, 0.90) and mother's use of multivitamin supplements for five or more

days during pregnancy (OR=0.23; 95% CI=0.07, 0.73). The odds ratio for drinking more than four glasses of tap water or drinks made from tap water per day during pregnancy was significantly elevated for leukemia in all ages combined (OR=3.43; 95% CI=1.18, 10.0). A significant inverse association was found for mother's use of multivitamin supplements for five or more days during pregnancy (OR=0.06; 95% CI=0.01, 0.57) and leukemia in children diagnosed prior to age five.

Significant inverse associations were found for nervous system cancers in all age groups and mother's weekly consumption of bacon, ham, or sausage during pregnancy (OR=0.15; 95% CI=0.03, 0.72), mother's weekly consumption of cured meat during pregnancy (OR=0.27; 95% CI=0.08, 0.88), and a child's consumption of lunch meat one or more times per week (OR=0.08; 95% CI=0.01, 0.76).

Significant inverse associations were found for brain and central nervous system cancers in all ages combined and mother's weekly consumption of bacon, ham, or sausage during pregnancy (OR=0.08; 95% CI=0.01, 0.65), child's consumption of lunch meat one or more times per week (OR=0.08; 95% CI=0.01, 0.79), and child's consumption of cured meat twice or more per week (OR=0.22; 95% CI=0.06, 0.79).

Figures 14a through 14d present the graphed dietary factors odds ratios for leukemia and for brain and central nervous system cancers. Prenatal dietary factors presented were primarily below 1.0 for both leukemia and brain and central nervous system cancers. Odds ratios for the category higher maternal tap water consumption during pregnancy were over 1.0 for leukemia and below 1.0 for brain and central nervous system cancers. Postnatal dietary factors were distributed around 1.0.

Exposure to Tobacco Smoke and Alcohol

Table 35 presents information on prenatal tobacco smoke and alcohol exposure and postnatal tobacco smoke exposure. During pregnancy, case and control mothers had similar rates of smoking, although case mothers who smoked reported smoking less cigarettes on average while pregnant (2,800) than control

mothers who smoked (3,640). Smoking in the home by other household members during the pregnancy was less common for case families (30%) than control families (41%). Case mothers also reported lower rates of any alcohol consumption during pregnancy than control mothers (20% vs. 32%).

Tables 36a through 36d present the odds ratios for tobacco smoke and alcohol exposures. Many of the tobacco smoke and alcohol exposure variables had relatively low prevalence of exposure. Exposure to prenatal tobacco smoke or alcohol or postnatal tobacco smoke did not appear to be associated with case status.

Figures 15a and 15b present the graphed odds ratios for tobacco smoke and alcohol exposure variables for leukemia and for brain and central nervous system cancers. The factors presented for this risk group appear to be distributed around 1.0.

Household-related Exposures: Chemical, Animals and Electromagnetic fields (EMFs)

Table 37 presents the prenatal and postnatal household-related exposure (chemicals, animals, and EMFs) information. The frequency of most prenatal household-related exposures were similar for case mothers and controls mothers. Car repair at home during pregnancy was higher for cases (25%) than controls (18%), while use of moth balls or moth crystals at home during pregnancy was lower for cases (15%) than controls (21%).

After the child was born, the frequency of several household-related exposures was slightly lower for cases than controls, including: yard and garden treatments (50% vs. 66%); use of oil based paints, thinners, brush cleaners, and strippers (25% vs. 41%); fingernail polish or remover (68% vs. 73%); living with a cat (20% vs. 34%); and living with a pet other than a dog or cat (26% vs. 35%). Cases had somewhat higher frequencies than controls for two postnatal variables: home car repair (35% vs. 26%) and regular use of a heated water bed (8% vs. 1%).

Tables 38a through 38d present the odds ratios for household-related

exposures. Two odds ratios were found to be significantly elevated for cancer incidence.   A significant inverse association was found for fingernail polish or remover use in the home during childhood and leukemia in all age groups (OR=0.38; 95% CI=0.14, 0.97). Both prenatal and postnatal use of an electric blanket, electric mattress pad, or heated water bed (household appliance EMF exposure) showed variability and low precision in odds ratio estimation, due to the low prevalence of these items. A child's regular use of an electric blanket, electric mattress pad, or heated water bed was significantly associated with leukemia for all ages combined (OR=12.0; 95% CI=1.25, 115) with only three case families and one control family reporting regular use during childhood.

Figures 16a through 16d present the graphed odds ratios for household-related exposure variables for leukemia and for brain and central nervous system cancers. The prenatal and postnatal household-related exposure factors appear to be randomly distributed around 1.0 with slightly more odds ratios below 1.0. The exception was a child's regular use of an electric blanket, electric mattress pad, or heated water bed which was elevated and had a very wide confidence interval.

Bivariate Analysis

To examine the potential for confounding of the estimated odds ratios for the environmental exposure factors, adjusted odds ratios were calculated. The effects of adjustment were evaluated for two exposure pathways of the primary study hypotheses (time-specific Parkway well field water and Ciba-Geigy ambient air emissions). They were analyzed in relation to each other, to the Ciba-Geigy pipeline variables, and to non-environmental factors for which associations with a cancer type was observed. Because associations were seen in this study primarily for female leukemia for exposures during the prenatal period, only results related to this case group and time period are discussed below. Due to the limited study size, time-specific Parkway well field water and Ciba-Geigy ambient air exposures were examined as two-level variables as noted below.

The unadjusted odds ratio for the prenatal time-specific Parkway well field water exposure (50% or more vs. less than 50%) for female leukemia, all ages combined, was 5.23. The unadjusted odds ratio for the prenatal Ciba-Geigy ambient air exposure (50th percentile and above vs. less than 50th percentile) for the same case group was 3.86. The adjusted odds ratios for both the prenatal time-specific Parkway well field water exposure and the prenatal Ciba-Geigy ambient air exposure decreased slightly relative to their unadjusted ratios when both variables were in the model (4.04 and 3.13, respectively).

The magnitude of the observed odds ratio for female leukemia for prenatal time-specific Parkway well field water exposure did not change appreciably when adjusted for child's antibiotic use, mother's consumption of cured meats during pregnancy, child's exposure to household appliance EMF, mother's prenatal tap water consumption, or mother's prenatal occupational exposure to dyes and pigments. The odds ratios were decreased, but remained elevated, after adjustment for living within one-half mile of the Ciba-Geigy pipeline in the prenatal period, mother's use of prenatal vitamins, number of mother's live births, or father's prenatal occupational exposure to petroleum products. The odds ratio was increased after adjustment for mother's prenatal occupational exposure to solvents.

The magnitude of the observed odds ratio for female leukemia for prenatal Ciba-Geigy ambient air exposure did not change appreciably when adjusted for living within one-half mile of the Ciba-Geigy pipeline in the prenatal period, child's antibiotic use, number of mother's live births, mother's consumption of cured meats during pregnancy, child's exposure to household appliance EMF, mother's prenatal tap water consumption, mother's prenatal occupational exposure to dyes and pigments, or mother's prenatal occupational exposure to solvents. The odds ratio decreased, but remained elevated, after adjustment for exposure to mother's use of prenatal vitamins. The odds ratio was increased after adjustment for father's prenatal occupational exposure to petroleum products.

Interview Study Strengths and Limitations

In considering the strengths and limitations of an epidemiologic study, it is important to consider the potential for "bias" (i.e., inaccuracy) in the estimated odds ratios or other outcome measures. Bias in measures of odds ratios can result from three sources: improper selection of study subjects; errors in exposure measurement or classification; and confounding (Steineck and Ahlbom, 1992). It is also important to consider the precision of odds ratio estimates, that is, the confidence that estimates are repeatable, and not subject to large random errors. Precision is strongly influenced by the size of the population study sample and the prevalence of exposure.

Selection Bias: If the cases or controls who participated in the study do not adequately represent the underlying study population, the odds ratio estimates may be biased positively or negatively (Rothman and Greenland, 1998). Because there was a 100% participation rate among eligible cases, selection bias for cases was not a problem.

Controls were randomly selected from the public school records of the Toms River School District. School rosters provide a close approximation of the underlying residential child population, since a high proportion of Dover Township children attend public schools (93%, according to 1990 U.S. Census data). Furthermore, the high participation rate among randomly chosen control families (80%) suggests that participating controls should be representative of the underlying population. Extensive search and recruitment procedures were effective in maximizing subject location and minimizing non-participation rates.

Table 39 compares the demographic characteristics of the 39 potential controls whose parents/guardians were not interviewed (i.e., those potential controls whose parents/guardians were never located, refused participation, or never responded) with the 159 interviewed controls. The characteristics of participating and nonparticipating controls were generally similar. Nonparticipants were found to have an earlier mean year of birth (1976 versus 1980), resided less frequently in Dover

Township at the time of the child's birth (23% versus 53%), and were less likely to be the mother's first born child (21% versus 41%) than participants. The nonparticipants and participants were similar for mean weight at birth (3,361 versus 3,352 grams), race (3% versus 3% nonwhite), and maternal age at the time of birth of the study child (26 versus 27 years). Participating and nonparticipating controls appeared to be very similar and, therefore, selection bias was unlikely .

It was important to assure that the matched controls selected for the 17 cases diagnosed prior to age 6 were Dover Township residents at both the time of the case's diagnosis and the time of entry into school. To address this issue, the school status of cases during the school year when their matched controls were selected from school rosters, was evaluated. School enrollment of the 17 cases diagnosed prior to school age is shown in Table 40. Eleven (65%) of the 17 cases were found on the Toms River School District rosters for the same year as their matched controls. Three case children diagnosed prior to school age were not found on the School District rosters from which their controls were selected. Three additional case children diagnosed prior to school age died prior to reaching first grade. These data show that cases and controls were similar in their residency duration in Dover Township from the date of case's diagnosis to entry into school.

Among the case children diagnosed after reaching school age (age 6 or more years), all 21 were found on the Toms River School District rosters in the same year from which their matched controls were selected. These data indicate that the public school records were a reliable source for identifying control children in this community.

Exposure Misclassification Bias: Odds ratio estimates may be biased by inaccurate classification of study subject exposures (Rothman and Greenland, 1998). When exposure classification errors are made similarly among cases and controls, the odds ratio estimate is more likely to show no increase in disease risk for that exposure. However, if exposure classification errors are more likely to be made in either cases or controls (differential misclassification), the odds ratio estimate may be

biased either higher or lower (Copeland et al., 1977).

Questionnaire-based information dependent on recall of past behaviors or experiences may be particularly susceptible to differential misclassification if cases are more or less likely to report specific exposures or activities. A Canadian study has reported that parental recall in a case-control study of childhood cancer can be differential under circumstances of enhanced public concern (Infante-Rivard and Jacques, 2000). A potential weakness of the Interview Study is that parents of cases may have differentially recalled their child's actual exposure histories, when compared with parents of control children. In order to minimize this bias, identical procedures for notification and interviewing all participants were employed; experienced interviewers were used; and copies of the questionnaire were not made available publicly until after the completion of all parental interviews. However, the consistency in the strength of the prenatal odds ratios for the high exposure category of time-specific Parkway well field water and the time-specific Parkway well field source/consumption index indicate that recall bias may have been a limited factor since mother's recall of water consumption did not appreciably change the observed strength of the association. Furthermore, there is no reason to believe that recall of mothers of female children with leukemia would have been more biased then the recall of mothers with male children with leukemia or mothers of children with other cancers.

With the exception of cancer diagnoses obtained from the State Cancer Registry, all medical information in the Interview Study was self-reported, and was not validated against medical records. Accuracy is dependent upon parental recall and knowledge of the requested medical information.

In order to assess the validity of Interview Study responses, data available from both parental interviews and birth certificates were compared for all cases born in New Jersey (n=32) and a random selection of controls born in New Jersey (n=53). Concordance for sex, race and categorical maternal age at birth were 100%. High concordance in both cases and controls (97% to 100%) was also seen for being the

first live birth of the mother and for categorical birth weight. Categorical number of prior pregnancies was less concordant (86% among cases and 85% among controls). Concordance of maternal address at time of the child's birth was 91% among cases and 96% among controls.

The environmental indices developed in the Interview Study were based on residential histories collected by interview. It is not expected that recall bias would be a problem for this type of information. Consequently, the residential-based exposure assessments are a strength in this study.

Confounding: Confounding bias occurs when the "background" risk of disease differs between the exposed and unexposed in the study population as a result of different distributions of risk factors other than the exposure of interest (Miettinen, 1974). A confounder or confounding variable is defined to be "...a factor that distorts the apparent magnitude of the effect of a study factor on risk. Such a factor is a determinant of the outcome of interest and is unequally distributed among the exposed and the unexposed" (Last, 2001). In this Report, unadjusted odds ratios are primarily presented for each factor without adjusting for potential confounding. Because of the relatively small study size, evaluation of potential confounding was either unable to be done or limited to bivariate analyses. Potential bias due to confounding by sex and/or year of birth was minimized by the Interview Study's matched design.

Precision: With a total of 40 cases, and with considerably fewer subjects in each cancer type and age grouping, odds ratio estimates from the Interview Study are inherently imprecise (i.e., the odds ratio estimates have wide confidence intervals). Using multiple controls per case (4 to 1) in this study serves to increase precision. However, inherent problems remain due to the low statistical power when evaluating multiple factors, which impacts the study's ability to identify modestly elevated odds ratios as statistically significant for the cancers of interest and any potential risk factor.

For example, when minimum detectable odds ratios (MDORs) were calculated

using the method of Schlesselman (1982), the Interview Study was determined to be able to detect associations of 2.8 and larger for a prevalence of exposure equal to 20% (assuming á=0.05, â=0.20). Given these assumptions, if the true odds ratio is 2.8 or larger, one would detect a statistically significant effect 80% of the time. If the odds ratio is lower than 2.8, the probability of detecting a statistically significant effect would be less than 80%. Using the same assumptions as above, other MDORs in the Interview Study ranged from 3.7 to 5.5 for smaller age and cancer groupings, such as leukemia in children under age five.

Multiple Comparisons: When researchers independently examine statistical associations for a large number of risk factors, it is likely that some number of false positive results will be found, due to the large numbers of comparisons conducted. While it is possible to statistically correct for this concern, it is controversial whether such corrections are needed (Savitz and Olshan, 1995; Thompson, 1998). We have chosen to present individual confidence intervals without adjustment for multiple comparisons.

In summary, the strengths of the Interview Study include the study's excellent response rates; cooperation of study families; and environmental exposure assessments based on residential information, calibrated water modeling and air modeling, and knowledge of completed exposure pathways. The limitations of the Interview Study include low statistical power and potential recall bias.

BIRTH RECORDS STUDY

Birth Records Study Methods

Geographic Area of Study: The geographic area for the Birth Records Study is Dover Township, New Jersey. Cases and controls were required to have mothers who resided within Dover Township at the time of the study child's birth.

Case Definition: In order to address community concerns of the potential of children moving away from Dover Township prior to being diagnosed with cancer, the Birth Records Study evaluated all types of childhood cancer. A case is defined as a child who: 1) was diagnosed with any type of cancer; 2) was under age 20 at the time of his or her diagnosis; 3) was diagnosed between January 1, 1979 and December 31, 1996; and 4) the child's mother must have been a resident of Dover Township at the time of the child's birth, based on birth certificate address information.

Case Identification: Childhood cancer cases (diagnosed 1979 - 1996 inclusive) from the New Jersey State Cancer Registry were matched against the birth records of the New Jersey Vital Statistics and Registration Office in order to determine those cases of childhood cancer diagnosed in New Jersey whose mothers were Dover Township residents at the time of the child's birth. To identify Dover Township births that may have been diagnosed with cancer after moving out of state, information on pediatric cancers was sought from ten out-of-state cancer registries including Florida, Pennsylvania, New York, Virginia, California, North Carolina, Georgia, Massachusetts, Delaware, and Texas. A list of all births in Dover Township from 1966 through 1996 compiled by the New Jersey Center for Health Statistics (CHS) was matched with records from these out-of-state cancer registries. The first year of available electronic birth data from the CHS is 1966.

Control Definition: Ten controls were selected for each case child and matched to the case as described below. The definition of a control child includes the

following: 1) the mother was a resident of Dover Township at the time of the child's birth; 2) the control was the same sex as the matched case; and 3) the control child was born in the same year as the matched case.

Control Selection: For each case, controls were randomly selected from all eligible births using the above matching criteria, from the electronic birth records (1966 onward) and paper birth records (prior to 1966) from the New Jersey Center for Health Statistics. None of the selected controls were identified as having cancer during the review of cancer registry data.

Data Collection: Information for this study consisted of data available on the study child's birth certificate and included: child's name, sex, date of birth, birth weight, APGAR score, and congenital malformations or anomalies of the child; the parent's race, ethnic origin, and highest education grade attained; and residence at time of birth; and mother's date of last menses, pregnancy history, number of prenatal doctor's visits, month prenatal care began, and usage of alcohol and tobacco products during pregnancy (only after 1988). In addition, information on the year of construction of the house where the parents resided at the time of the child's birth was collected from Dover Township municipal records.

Analytic Methods: Data analyses were conducted in the manner described previously for the Interview Study. The case groupings for the Birth Records Study include: all cancers combined (all cases); leukemia; all nervous system cancers; brain and central nervous system cancers; and all other cancers. As in the Interview Study, the Birth Records Study children were divided into two age groups within each cancer grouping: children diagnosed prior to age 20 (all cases) and children diagnosed prior to age five. Only the pregnancy period was evaluated in the Birth Records Study. It was assumed that the mother's residence at the time of the child's birth was the mother's residence throughout the pregnancy period. Adequacy of prenatal care utilization was evaluated using the Kotelchuck method (1994). The Kotelchuck method attempts to characterize the adequacy of prenatal care utilization on two independent and distinctive dimensions: prenatal care initiation and the number of

prenatal visits.

Birth Records Study Results

Matching of the New Jersey State Cancer Registry (SCR) records from 1979 through 1996 against the New Jersey Vital Statistics and Registration Office's birth records identified a total of 48 children with cancer born to mothers living in Dover Township at the time of the child's birth. Table 41 presents a summary of where these children resided at the time of their diagnoses. Of the 48 cases, 41 were residents of Dover Township when diagnosed with cancer, five of the cases resided in another Ocean County community, and one resided in another New Jersey county at the time of diagnoses. Of the 41 cases who were residents of Dover Township both at birth and at diagnosis, 24 were diagnosed with leukemia or nervous system cancer, and thus were also included in the Interview Study.

Electronic birth record data matching with out-of-state cancer registries was completed for nine of ten registries approached (Florida, Pennsylvania, New York, Virginia, California, North Carolina, Massachusetts, Delaware, and Texas) and did not find any additional cases. One registry (Georgia) denied access on the basis of confidentiality concerns. Information on one case diagnosed while living in another state was provided by the SCR.

Table 42 presents the age of diagnosis and cancer type of the 48 eligible cases. Leukemia accounted for 16 of the cases (33%), while nervous system cancers accounted for 13 of the cases (6 or 13% overall were sympathetic nervous system cancers and 7 or 15% overall were brain and central nervous system cancers). The other cancers include: five lymphoma cases (10%); four soft tissue sarcoma cases (8%); two renal cancer cases (4%); two melanoma cases (4%); and one case each of thyroid cancer, nasopharyngeal cancer, gonadal germ-cell tumor, other specified malignant tumor, other unspecified malignant tumor, and cancer in-situ of the cervix.

Controls were randomly selected from New Jersey birth records for Dover Township. Ten controls were selected for each case and matched on the case's year

of birth and sex. Birth certificates for all children were photocopied and residential addresses inspected to ensure complete information. Three selected controls with missing address information (two listed P.O. boxes and one was blank) were replaced with other randomly selected controls. Over 99% of the originally selected controls were used in the study (477/480).

Environmental Factors

Household Drinking Water Source Exposure

Private Well Assessment: Of the total 528 study children in the Birth Records Study, 99 could not be assigned to the public water distribution system and were therefore assumed to have had a private water source (see Volume IV, Appendix D). Table 43 presents frequency information for case and control birth residences that were determined to have private well water and were located in one of 11 groundwater regions with a history of groundwater contamination within Dover Township. Only two of the 48 cases (4.2%) were found to reside at the time of their birth in any of the regions. One case child resided within the Breton Harbors region, and one case child resided in the North Maple Avenue region at the time of birth. A similar percentage of control children, 20 out of 480 (4.2%), were found to reside at the time of their birth in any of the regions.

Table 44 presents odds ratios for birth residence in any of the 11 Dover Township groundwater regions. Exposure to private wells in contaminated regions did not appear to be associated with case status.

Public Water Source Assessment: Table 45 presents exposure index frequency information for ten public water well field sources serving case and control birth addresses. The water source indices were derived by averaging the monthly computer modeled estimates for the prenatal period (8 months prior to the birth month and the birth month itself). Since each residence hooked up to the public distribution system in Dover Township could receive water from one or more public well field, cases and controls were divided into three exposure categories: low

(receiving less than 10% of their drinking water from the specified public well field); medium (receiving 10% to 49.9% of their water from the specified public well field); and high (receiving 50% or more of their water from the specified public well field). These cut points were chosen to differentiate little or no residential exposure to a public well field from significant potential exposure (i.e., 50% or more of all water delivered to that residence). Other cut points were also examined and discussed below.

As seen in Figure 17 and Table 45, two well fields (Holly Street and Parkway) supplied the greatest percentage of drinking water to the largest number of case and control birth homes. The Parkway well field supplied the greatest amount of water to study homes, with 56% of the case children and 54% of the control children supplied with 10% or more of their water from this source. Holly Street well field supplied 56% of the cases and 49% of the controls with 10% or more of their water from this source. A small number of case and control birth homes received medium to high amounts of water from three well fields (Brookside, Indian Head, and Route 70). The remaining well fields (Anchorage, Berkeley, Silver Bay, South Toms River and Windsor) supplied a negligible amount of drinking water to the case and control birth homes.

Tables 46a through 46e present odds ratios for the Brookside, Holly Street, Indian Head, Parkway and Route 70 well fields. The five well fields for which odds ratios are presented were chosen because they supplied the bulk of the water to study residences. Odds ratios for the remaining five well fields (Anchorage, Berkeley, Silver Bay, South Toms River, and Windsor) were calculated, but are not presented in this report, as the number of cases and controls in the medium and high exposure categories were generally too sparse to generate odds ratios.

The medium exposure category for the Brookside well field was significantly associated with all cancers and all ages combined (OR=2.30; 95% CI=1.02, 5.19). Exposure to other well fields in which odds ratios could be calculated did not appear to be associated with case status. Figures 18a and 18b present graphed odds ratios

by well field for leukemia and for brain and central nervous system cancers.

Although not presented, two other approaches based on the control distribution were used to create alternate variables. The first approach was a tertile cut point using the distribution of the control population. The second approach was a low (0%), medium (greater than 0% to 49.9%), and high (50+%) cut point distribution. Exposure categories calculated using these alternative cut points did not appear to be associated with case status, or display very different odds ratios from those calculated using the initial cut point approach.

Odds ratios were also calculated separately for males and females. Tables 47a through 47e present odds ratios for well field source by sex. Exposure to these well fields did not appear to be associated with case status when evaluated separately by sex.

Because of documented groundwater contamination of the Parkway and Holly Street well fields, odds ratios were also calculated with temporal adjustments regarding the possible period of contamination of the Parkway well field and the Holly Street well fields (as previously discussed in the Interview Study results). Odds ratios for the Parkway (exposures limited to 1982 and later) and Holly Street (exposures limited to 1975 and earlier) well fields were calculated and presented in Tables 48a through 48e. Although not statistically significant, odds ratios for the medium (OR=3.63; CI=0.32, 41.8) and high (OR=2.72; CI=0.26, 28.1) time-specific Parkway well field categories for leukemia were elevated. Similarly, the odds ratios for the medium (OR=6.24; CI=0.60, 64.8) and high (OR=7.48; CI=0.65, 86.4) time-specific Holly Street well field categories for all other cancers were elevated.

In addition, odds ratios for the Parkway and Holly Street time-specific indices were calculated by sex and presented in Tables 49a through 49e. For females with leukemia, the odds ratios for the medium (OR=3.90; CI=0.34, 45.2) and high (OR=2.15; CI=0.19, 24.1) time-specific Parkway well field categories remained slightly elevated. For all other cancers, the odds ratios for the medium (OR=5.50;

CI=0.48, 62.9) and high (OR=5.28; CI=0.37, 75.9) time-specific Holly Street well field categories for males were elevated.

Exposure to Air Pollution from Point Sources

Table 50 shows the mean frequencies of all case and control children's estimated exposures during the pregnancy period to two point source air pollution emitters, the Ciba-Geigy facility and the Oyster Creek Nuclear Generating Station, over the relevant total study interval. The cut points for the low, medium and high categories in Table 50 were determined using the 50th and 75th percentile values within the control population. The three categories of exposure for estimated ambient air emissions from Ciba-Geigy are: less than 1.50; 1.50 to 3.04; and greater than 3.04 relative air impact units. The three categories of exposure for estimated ambient air emissions from the Oyster Creek are: less than 0.065; 0.065 to 0.44; and greater than 0.44 fCi/m^3. Details concerning the model and construction of the estimated indices for these two point source air pollution emitters are found in Appendix F, in Volume IV.

Table 51a through 51e present odds ratios for the estimated average exposure to ambient air emissions for Ciba-Geigy. Exposure to medium or high Ciba-Geigy ambient air categories did not appear to be associated with case status. Graphed odds ratios for exposure to Ciba-Geigy ambient air emissions are presented for leukemia and for brain and central nervous system cancers (Figure 19).

Table 51a through 51e present odds ratios for the estimated average exposure to ambient air emissions for Oyster Creek. Exposure to medium or high Oyster Creek ambient air categories did not appear to be associated with case status. The graphed odds ratios for exposure to Oyster Creek ambient air emissions (Figure 20) fluctuate close to 1.0.

Table 52a through 52e present odds ratios for the estimated average for exposure to Ciba-Geigy and Oyster Creek airborne gas emissions by sex. The odds ratio for the high category for Ciba-Geigy ambient air was significantly elevated for

all females diagnosed with any type of cancer prior to age five (OR=6.07; CI=1.34, 27.4). The significant elevation for all females diagnosed under five appears to be driven by the elevated odds ratio for the high Ciba-Geigy ambient air exposure category for females with leukemia (OR=7.78; CI=0.78, 77.4).

Other Environmental Factors

Residential Proximity to Sites of Concern: Table 53 presents the number of case and control children whose birth residence was within one-half mile of a site of concern. Few children had birth residences within one-half mile of any of the sites. Although 9 cases (19%) and 86 controls (18%) had birth residences within one-half mile of the Ciba-Geigy pipeline, only two cases (4%) and seven controls (2%) had birth residences within one-half mile of any of the pipeline breaks during or after the year of the breaks. No cases and few controls had birth residences within one half-mile of three of the sites of concern (Reich Farm, the Dover Township Municipal Landfill, and the Ocean County Landfill).

Tables 54a through 54e present the odds ratios for a birth residence in proximity to a site of concern. Birth residence within one-half mile of the Ciba-Geigy pipeline was significantly associated with all other cancers for children diagnosed prior to age five (OR=10.2; CI=1.61, 64.5). However, no case or control children in this category (all other cancers) had a birth address within one-half mile of any pipeline break. Figure 21 graphically presents odds ratios for leukemia and proximity to sites of concern.

Tables 55a through 55e present the odds ratios for a birth residence in proximity to a site of concern by sex. Birth residence within one-half mile of a Ciba-Geigy pipeline break was significantly associated with all cancers combined for female children (OR=6.67; CI=1.11, 39.9). Birth residence within one-half mile of Ciba-Geigy was significantly associated with all cancers combined for female children diagnosed prior to age five (OR=15.7; CI=1.38, 179). Birth residence within one-half mile of the Ciba-Geigy pipeline was significantly associated with all other cancers

for female children (OR=5.02; CI=1.08, 23.3).

Birth Residence Year of Construction: Of the 528 birth residences, information on the year of construction was available from municipal records for 438 homes (83%). For all study children with a birth residence of known year of construction, cases and controls had nearly equal percentage of older homes (64% vs. 62%). While older residences were not statistically significantly associated with any of the cancer groupings, the odds ratio for brain and central nervous system cancers was elevated fourfold (OR=4.29; CI=0.46, 40.4).

Environmental Index Correlations

The environmental risk factor indices for the primary study hypotheses (exposure to time-specific Parkway well field water, exposure to time-specific Holly Street well field water, and exposure to Ciba-Geigy ambient air emissions) were evaluated for their correlation with other public well field waters, proximity to sites of concern, and Oyster Creek ambient air emissions. The significant correlations coefficients (p<.01) for the prenatal time period are presented in Table 56.

The time-specific Parkway well field index was statistically inversely correlated with the time-specific Holly Street well field index (r=-0.23), the Ciba-Geigy ambient air index (r=-0.16), the Oyster Creek ambient gas index (r=-0.28), the proximity to Ciba-Geigy index (r=-0.12), and the Brookside well field index (r=-0.20). The time-specific Parkway well field index was statistically correlated with the Route 70 well field index (r=0.15). Unlike the Interview Study, the time-specific Parkway well field index was not statistically correlated with the proximity to Ciba-Geigy pipeline index or the proximity to Ciba-Geigy pipeline breaks index.

The time-specific Holly Street well field index was statistically correlated with the Ciba-Geigy ambient air index (r=0.24), the proximity to Ciba-Geigy index (r=0.22), the proximity to the section of the Toms River index (r=0.20), and the proximity to the Coal Gas site index (r=0.15) and statistically inversely correlated with the Route 70 well field index (r=-0.15).

The Ciba-Geigy ambient air index was statistically correlated with the proximity to Ciba-Geigy index (r=0.71), the proximity to the section of the Toms River index (r=0.40), the Indian Head well field index (r=0.56), and the Route 70 well field index (r=0.21), and statistically inversely correlated with both the South Toms River well field index (r=-0.15) and the Brookside well field index (r=-0.17).

As in the Interview Study, many of the environmental risk factor indices were significantly correlated with each other.

Other Factors

Demographic, Pregnancy and Birth Characteristics

Table 57 presents demographic, pregnancy and birth characteristics of the study population as available from the birth certificate. There were nearly an equal number of male and female cases (23 and 25 respectively). When parent's race was known, virtually all case and control parents were white (97%). The period 1980-84 had the highest number of case births, 14 (29%), while the period 1985-90 had the highest number of case diagnoses, 22 (46%).

In general, the frequency of most of the demographic, pregnancy, and birth characteristics did not differ by case status. Paternal education differed slightly by case and control group with 19% of the case fathers and 27% of the control fathers having 16 or more years of education. Mother's pregnancy histories differed by case and control group for one or more prior pregnancies of the mother (83% vs. 67%). Complications of the mother's pregnancy with the child was slightly higher for case mothers than control mothers (23% vs. 18%) while any complications of labor or delivery were slightly lower for case mothers than control mothers (21% vs. 26%). The percentage of children who were first live births of their mother differed by case (19%) and control (39%) group. The average birth weight for cases (3,602 grams) was higher than for controls (3,407 grams).

Tables 58a through 58e present the odds ratios for the demographic, pregnancy, and birth characteristic variables. Almost all odds ratios for being the first

live birth of the mother were below 1.0. Being the first live birth was statistically significantly low for all cancers in all ages combined (OR=0.35; 95% CI=0.16, 0.75) and the all other cancer group in all ages combined (OR=0.18; 95% CI=0.04, 0.83).

The odds ratios for having less than adequate prenatal care utilization were generally mixed, but significantly elevated for leukemia in all ages combined (OR=3.81; 95% CI=1.16, 12.5) and leukemia in children diagnosed prior to age five (OR=16.6; 95% CI=1.79, 154). A significant inverse association was found for having less than adequate prenatal care utilization and nervous system cancers in all ages combined (OR=0.12; 95% CI=0.01, 0.95).

Odds ratios for birth weights of 4000 grams or higher were nearly all above 1.0. High birth weight was significantly associated with leukemia in children diagnosed prior to age five (CI=5.66; 95% CI=1.07, 29.9).

Mother's and father's educational level displayed mixed odds ratios. Low maternal education (less than 12 years) was significantly associated with leukemia in children diagnosed prior to age five (OR=8.33; 95% CI=1.23, 56.6).

The odds ratio for any complications of pregnancy with the child was elevated for brain and central nervous system cancers in children diagnosed prior to age five (OR=6.71; 95% CI=0.91, 49.5) and significantly elevated for nervous system cancer in children diagnosed prior to age five (OR=4.94; 95% CI=1.26, 19.4). The types of pregnancy complications on the birth certificate varied substantially and provided no clear insight into the meaning of these results.

Figures 22a and 22b present the graphed odds ratios for demographic, pregnancy, and birth characteristics by leukemia and brain and central nervous system cancers.

Exposure to Tobacco Smoke and Alcohol

Table 59 presents the tobacco smoke and alcohol exposures of the study population. Since this information was not collected on New Jersey birth certificates until 1989, nearly 90% of the study subjects had no data. Because of the sparsity of

data for these variables, no odds ratios were calculated.

Bivariate Analysis

To examine the potential for confounding of the estimated odds ratios for the environmental exposure factors, adjusted odds ratios were calculated. The effects of adjustment were examined for two exposure pathways of the primary study hypotheses: time-specific Parkway well field water exposure and Ciba-Geigy ambient air exposure. They were analyzed in relation to each other, to the Ciba-Geigy pipeline exposure variables, and to adequacy of prenatal care utilization. Because of the limited study size, for the purposes of these analyses, time-specific Parkway well field water and Ciba-Geigy ambient gas exposures were examined as two-level variables as noted in the Interview Study above.

The unadjusted odds ratio for the prenatal time-specific Parkway well field water exposure (50% or more vs. less than 50%) for female leukemia, all ages combined, was 1.08. The unadjusted odds ratio for the prenatal Ciba-Geigy ambient air exposure (50th percentile and above vs. less than 50th percentile) for the same case group was 1.38. The adjusted odds ratios for both the prenatal time-specific Parkway well field water exposure and the prenatal Ciba-Geigy ambient air exposure increased slightly relative to their unadjusted ratios when both variables were in the model (1.21 and 1.43, respectively). In general, the adjustment of prenatal time-specific Parkway well field water exposure and prenatal Ciba-Geigy ambient air exposure relative to the Ciba-Geigy pipeline exposure variables and to adequacy of prenatal care utilization the other did not substantially change the magnitudes of the odds ratios calculated in the unadjusted analyses.

Birth Records Study Strengths and Limitations

In considering the strengths and limitations of an epidemiologic study, it is important to consider the potential for "bias" (i.e., inaccuracy) in the estimated odds ratios or other outcome measures. Bias in measures of odds ratios can result from

three sources: improper selection of study subjects; errors in exposure measurement or classification; and confounding (Steineck and Ahlbom, 1992). It is also important to consider the precision of odds ratio estimates, that is, the confidence that estimates are repeatable, and not subject to large random errors. Precision is strongly influenced by the size of the population under study and the prevalence of exposure.

Selection Bias: If the study cases or controls do not adequately represent the underlying population, the odds ratio estimates can be biased positively or negatively (Rothman and Greenland, 1998). Case ascertainment for the Birth Records Study used the New Jersey State Cancer Registry, a population-based cancer registry with virtually complete cancer ascertainment (estimated to be greater than 99% complete) during the study period. In addition, attempts were made to find children who were born in Dover Township and then migrated to other states before diagnosis, by reaching out to cancer registries of ten other states. The nine states that provided data were the destination of 70% of Ocean County out-migrants between 1985 and 1990, according to U.S. Census data. It is possible that eligible individuals, whose mothers were Dover Township residents at the time of their birth, may have developed cancer prior to their 20th birthday while residing outside of the U.S., or in one of the states where matching was not performed. However, we have no reason to believe that the case series for this study is not representative of all possible cases.

The controls in the Birth Records Study were randomly selected from a population-based sampling frame (birth certificate records for the State of New Jersey) which includes the entire population of births among Dover Township residents. Since only three of the 483 randomly selected birth certificates (less than one percent) had to be excluded because of inadequate address information, the Birth Records Study's controls can be considered to be a representative sample of the underlying population and, therefore, selection bias was unlikely.

Exposure Misclassification Bias: Odds ratio estimates may be biased by inaccurate classification of study subjects on exposure status (Rothman and

Greenland, 1998). When exposure classification errors are made similarly among cases and controls, the odds ratio estimate is more likely to show no increase in disease risk for that exposure. However, if exposure classification errors are more likely to be made in either cases or controls (differential misclassification), the odds ratio estimate may be biased either higher or lower (Copeland et al., 1977). In the Birth Records Study, all information was collected at the time of birth directly from the parents or from maternal or child medical charts. These data could not be susceptible to any potential errors caused by differential recall between cases and controls. It was assumed that the mother's residence at the time of the child's birth was the mother's residence throughout the entire pregnancy period, which could lead to exposure misclassification. In the Interview Study, 81% of study mothers lived in the same residence throughout their pregnancy.

The environmental indices developed in the Birth Records Study were based on residential information extracted from the birth certificate. Therefore, recall bias is applicable to this type of information. Consequently, the residential-based exposure assessments are a strength in this study. However, since information on the source of drinking water (public or private well) for the residence is not on the birth certificate, residences were assumed to be connected to the UWTR system unless water distribution pipes were not located near the residence during the year of the child's birth. Thus potential error could occur in assignment of a home to public or private water, and this is a possible limitation in the Birth Records Study.

Confounding: Confounding bias occurs when the "background" risk of disease differs between the exposed and unexposed in the study population as a result of different distributions of risk factors other than the exposure of interest (Miettinen, 1974). In this Report, unadjusted odds ratios are primarily presented, without adjustment for potential confounders. Because of the relatively small study size, evaluation of potential confounding was limited to bivariate analyses or could not be calculated. In the Birth Records Study, potential bias due to confounding by sex and year of birth was minimized in the design through matching.

Precision: With 48 cases and 480 controls overall, and with fewer subjects in each cancer subset and age grouping, odds ratio estimates from the Birth Records Study are inherently imprecise (i.e., the odds ratio estimates have wide confidence intervals). Using ten controls per case in this study served to increase precision. However, inherent problems remain due to the low statistical power when evaluating multiple factors, which impacts the study's ability to identify modestly elevated odds ratios as statistically significant for the cancers of interest and any potential risk factor.

For example, when minimum detectable odds ratios (MDORs) were calculated using the method of Schlesselman (1982), the Birth Records Study was found to be able to detect associations of 2.4 and larger for a prevalence of exposure equal to 20% (assuming á=0.05, â=0.20). Given these assumptions, if the true odds ratio is 2.4 or larger, you would detect a statistically significant effect 80% of the time. If the odds ratio is lower than 2.4, the probability of detecting a statistically significant effect would be less than 80%. Using the same assumptions as above, other MDORs in the Birth Records Study ranged from 3.6 to 7.5 for smaller age and cancer groupings, such as leukemia in children under age five.

Multiple Comparisons: When researchers independently examine statistical associations for a large number of risk factors, it is likely that some number of false positive results will be found, due to the large numbers of comparisons conducted. While it is possible to statistically correct for this concern, it is controversial whether such corrections are needed (Savitz and Olshan, 1995; Thompson, 1998). We have chosen to present individual confidence intervals without adjustment for multiple comparisons.

In summary, the strengths of the Birth Records Study include: the data used is free of exposure misclassification due to recall error, since all data were recorded on the birth certificate around the time of birth; case and control selection was unbiased; and the environmental exposure assessments were based on birth certificate

residence information. Limitations of the Birth Records Study include: no information on the child's postnatal exposures was available; limited prenatal information; no parental occupational information was available; the residence listed on the birth certificate was assumed to be the residence for the entire pregnancy period; assigned water source was not verified by resident; and the study's low statistical power.

DISCUSSION

Introduction

Previous NJDHSS analysis of childhood cancer incidence found a statistically significant elevation of childhood cancer in Dover Township, particularly for leukemia, and brain and central nervous system cancers in female children (Berry and Haltmeier, 1997). The current study was specifically designed to explore the relationship between distinctive environmental factors for this community and selected childhood cancers.

During the environmental evaluation phase of the Public Health Response Plan, several environmental exposure pathways that might impact Dover Township residents were documented. The primary hypotheses in this study were that childhood cancers were associated with these environmental exposure pathways which were identified in earlier reports and include:

- contamination of potable water from UWTR Parkway well field by the Reich Farm Superfund site (possibly as early as 1982);
- contamination of potable water from UWTR Holly Street well field, due to wastewater discharge into the Toms River from the Ciba-Geigy site (from the mid-1960s, possibly ending by 1975);
- contamination of potable water affecting private wells near the Reich Farm and Ciba-Geigy sites and other areas in Dover Township from other or unknown sources; and
- air pollution emissions from the Ciba-Geigy facility.

Potential exposure to other environmental factors were also considered in order to address additional community concerns. These environmental factors include:

- potential exposure to ambient air releases from the Oyster Creek Nuclear

Generating Station, located approximately ten miles south of Dover Township;

- residential proximity to sites in the area which concerned the community:

  < the Ciba-Geigy Superfund site,

  < a section of the Toms River where treated wastewater was discharged (1952 to 1966) from the Ciba-Geigy facility,

  < the Ciba-Geigy pipeline which transported treated wastewater across the Township (1966 to 1991) and experienced three documented breaks during its usage,

  < the Reich Farm Superfund site,

  < the Dover Township Municipal Landfill,

  < the Ocean County Landfill, and

  < the Toms River Coal Gas site; and

- age of residence at birth.

One of the most challenging and important components of an epidemiologic study is the assessment of past environmental exposures (see Volume IV, Appendix I). In this study, computer modeling was used to derive monthly estimates of the percent of water delivered to each study residence from each UWTR well field in the public water distribution system from 1962 through 1996 (see Volume IV, Appendix D). In addition, computer modeling was used to derive monthly estimates of potential exposure at each study residence to ambient air emissions from two facilities in the Dover Township area, Ciba-Geigy and Oyster Creek Nuclear Generating Station, from 1962 through 1996 (see Volume IV, Appendix F). From these monthly modeled data, average exposure indices were calculated for each study subject using historical residential information. The monthly modeled data and the indices were calculated without knowledge of the study subjects case or control status.

Although computer modeling of the public water distribution system was the most objective method available to estimate past exposure to well field water (the vehicle for the actual distribution of environmental contaminants), there are

limitations in this approach to exposure assessment. In developing the historic model reconstructions, a number of assumptions were made on how the system operated over time (ATSDR, 2001). Altering system operations, such as when wells were pumping, might affect the estimated percentage of water delivered to a particular location from any well field. In order to evaluate the uncertainty and variability in system operations, ATSDR used multiple system assumptions to assess water exposure percentage estimates. This sensitivity analysis found that estimates did not vary greatly, with the annual standard deviation of the differences always less than ten percent and frequently less than five percent (ATSDR, 2001). Consequently, the use of computer modeling for the water exposure assessment was a strength in this study.

Similarly, computer modeling was used to derive air pollution exposure estimates for Ciba-Geigy facility and Oyster Creek. As with the water distribution system modeling, this was the most objective method available to estimate the past exposure emissions to air pollutants from these facilities. However, the quality of input data for the air models was not considered to be as high quality as in the water modeling. This was particularly true for the Ciba-Geigy models where actual emission data was unavailable and Atlantic City weather data were used. In an effort to address the missing emission data, annual production information for the Ciba-Geigy facility was used to modify the monthly exposure estimates used in the exposure assessment. Additionally, EOHSI conducted sensitivity analyses using weather data available for a portion of the study period from a closer weather station (Lakehurst) and also used a different model to calculate estimates for comparison. In general, both the use of a different model and the use of closer weather data produced higher exposure estimates than the data used for the exposure assessments (EOHSI, 2001). Exposure estimates for Oyster Creek were considered better since they were generated using actual emission data and on-site weather information.

Another strength of the Interview Study was its ability to evaluate potential exposure during specific critical time periods. Exposure indices were created for each

study subject during three time periods: the total study time period (one year prior to birth to the date of diagnosis); the prenatal time period; and the postnatal time period. For the Birth Records Study, only exposures at the birth residence were evaluated for the prenatal period, since no other exposure data were available.

Residential distance within one-half mile of seven sites of concern was also evaluated. Because relatively few study children ever lived within one-half mile of a site of concern, an index of ever/never having lived near each site of concern was used, rather than the percent of time a child lived near the site. For the Interview Study, as with the modeled data, exposure indices for ever having lived within one-half mile of a site of concern were created for three time periods: the total study time period (one year prior to birth to the date of diagnosis); the prenatal time period; and the postnatal time period. For the Birth Records Study, only the prenatal period was evaluated using address at the time of birth.

Residential proximity to a site was not specific to an exposure pathway, as it was with the air and water modeling, or groundwater plume shape, but it might capture other routes of exposure that could not be accounted for in the more sophisticated assessments, such as potential exposure through contact with the site. In general, the indices developed using proximity to sites of concern should be considered to be a less accurate estimate of potential exposure than those indices derived using the computer model estimates.

As with any epidemiologic study, the results in this Final Report should be interpreted carefully and in conjunction with existing biological and epidemiologic knowledge. Due to the low statistical power of the study, the analyses are sensitive to random fluctuations in numbers, which results in substantial imprecision in the odds ratios (reflected by wide confidence intervals).

The purpose of the following section on Risk Factor Evaluation is to discuss the findings in terms of the patterns and magnitude of the exposure odds ratios, the consistency between the Interview and Birth Records Studies, and consistency with previous studies conducted in other populations.

As noted earlier, the environmental risk factors correspond to potential environmental exposure pathways identified in this community and represent the study's primary hypotheses. Information on other factors, collected from questionnaires (Interview Study) or birth certificates (Birth Records Study) were included because they are factors which are traditionally studied, potential risk factors, or potential confounders of the environmental factors.

Risk Factor Evaluation

<u>**Environmental Factors**</u>

Household Drinking Water Source Exposure

Three major study hypotheses were evaluated: exposure to private well water in areas with known groundwater contamination; exposure to Holly Street well field water; and exposure to Parkway well field water. Since historical contamination of the Holly Street and Parkway well fields has been documented (NJDHSS and ATSDR, 2001a; NJDHSS and ATSDR, 2001b; NJDHSS, NJDEP, and ATSDR, 2001), potential human exposure to the contaminated groundwater became one of the key study questions to be examined. Exposure to water from the eight additional UWTR well fields (Anchorage, Berkeley, Brookside, Indian Head, Route 70, Silver Bay, South Toms River, and Windsor) was also evaluated.

Private Well Water: For both the Interview and Birth Records Study, few study children ever lived in a household with a private well in any of the 11 groundwater regions with documented contamination. In general, exposure to private wells in any groundwater region did not appear to be associated with childhood cancer incidence. However, in the Interview Study the odds ratios for ever using drinking water from a private well in any of the 11 groundwater regions for the total time and postnatal time were both over 5.0 for leukemia. The elevated odds ratios were based on two case children (1 male and 1 female), both with leukemia, whose homes had private wells but were located in two different groundwater regions. The prenatal leukemia odds ratio could not be calculated since there were

two cases but no controls with drinking water from a private well usage in any of the groundwater regions during that time period.

Holly Street and Parkway Well Fields: Time-specific indices for Holly Street and Parkway well fields water exposure were calculated with temporal adjustments regarding the possible period of contamination of these well fields. In both the Interview and the Birth Records Study, exposure to time-specific Holly Street well field did not appear to be associated with leukemia or brain and central nervous system cancers. Few of the case children in either of the studies were in the medium or high time-specific Holly Street well field water exposure categories, and none of the cases diagnosed prior to age five were in those categories. The lack of any association of Holly Street well field water and childhood cancer could be due in part to the cessation of the exposure pathway early in the study period (assumed to have ended no later than 1975), so that only a small number of study subjects could potentially have had exposure.

While exposure to time-specific Parkway well field water did not appear to be associated with leukemia or brain and central nervous system cancers when both males and females were analyzed together, separate analyses of time-specific Parkway well field exposure by sex revealed a noticeable pattern in the odds ratios. In the Interview Study, an elevated prenatal exposure odds ratio for females diagnosed with leukemia was found for the high exposure category of time-specific Parkway well field water (OR=5.0) and a statistically significant elevation was seen for females with leukemia in the high exposure category for the prenatal time-specific Parkway well field source/consumption index (OR=6.0). While the addition of tap water consumption to the water source variable only modestly increased the odds ratio, the time adjustment noticeably increased both the unadjusted water source and the unadjusted water source/consumption variable odds ratios with the latter becoming statistically significant.

Eight annual incremental adjustments to the possible contaminant time window revealed that odds ratios remained elevated for all of the high exposure categories of

the alternate prenatal time-specific Parkway well field water variable for females diagnosed with leukemia, with the 1984-1996 exposure period displaying the highest odds ratio (OR=15). Of note, female leukemia cases in the high prenatal Parkway well field exposure category were all born after 1983.

Although no associations were detected in analyses of the overall study population, the result for females diagnosed with leukemia is consistent with the study's a priori hypothesis that exposure to Parkway well field water during the time-specific interval was a risk factor for childhood leukemia.

In the Birth Records Study, odds ratios for females with leukemia were slightly elevated for the medium and high time-specific Parkway exposure categories (OR=3.6 and 2.7, respectively). Time-specific Parkway well field source/consumption indices could not be created in the Birth Records Study, since tap water consumption information was not available.

Postnatal exposure to time-specific Parkway well field water did not appear to be associated with leukemia in females. Prenatal and postnatal exposure to time-specific Parkway well field water did not appear to be associated with leukemia in males. Additionally, prenatal or postnatal exposure to time-specific Parkway well field water did not did not appear to be associated with brain and central nervous system cancers.

To examine the potential for confounding of the estimated odds ratio for time-specific Parkway well field water prenatal exposure for female leukemia, adjusted odds ratios were calculated in relation to the Ciba-Geigy ambient air exposure variable, the Ciba-Geigy pipeline exposure variables, and the non-environmental factors for which associations with leukemia were observed. In general, after adjustment for these factors the Interview Study odds ratio for the prenatal time-specific Parkway well field water remained elevated.

The chemical composition of the groundwater contamination which resulted from the dumping of wastes at Reich Farm had not been well characterized in the past. A variety of chemicals including trichloroethylene, tetrachloroethylene, and a

previously unknown material, styrene-acrylonitrile (SAN) trimer, have been found in the plume (NJDHSS and ATSDR, 2001b). However, since the concentration of the contaminants impacting the Parkway well field over the years is unknown, the risk to the community is not well understood. Consequently, the true carcinogenic potential of the contamination mixture in this completed exposure pathway remains unknown.

The underlying biological basis for the excess of female leukemia found in this study is unclear. A previous study by the New Jersey Department of Health (Cohn et al., 1994) found that the rate of leukemia in female children was elevated in New Jersey towns with a history of trichloroethylene-contaminated community drinking water, compared to towns without contamination.

Previous studies in Woburn, Massachusetts have reported an association between access to municipal drinking water contaminated with several chlorinated organics and childhood leukemia, prenatal deaths, birth defects and childhood disorders (Lagakos et al, 1986). A subsequent follow-up study by the Massachusetts Department of Public Health (1997) of 21 childhood leukemia cases in Woburn concluded that the incidence of childhood leukemia was associated with potential maternal exposure to water from the contaminated wells during pregnancy, particularly during the second and third trimesters. No excess leukemia risk was seen for exposure to the contaminated municipal wells in Woburn from birth to the date of cancer diagnosis. In contrast to the findings in this study which suggest a female leukemia excess in association with exposure to time-specific Parkway well field water, the Woburn study included primarily male leukemia cases (76% of the 21 cases).

A Canadian case-control study of exposure to drinking water contaminants (trihalomethanes, selected metals, and nitrates) did not find any association between prenatal exposure and childhood leukemia, but reported modest associations of childhood leukemia and postnatal exposure to trihalomethanes, chloroform, and zinc (Infante-Rivard et al., 2001). A case-control study of 540 children with brain tumors did not find a consistent pattern of association between use of a well during

pregnancy as the source of residential water and subsequent risk of brain tumors during childhood (Mueller et al., 2001).

Other United Water Toms River well fields: Although analyses of the eight other UWTR well fields (Anchorage, Berkeley, Brookside, Indian Head, Route 70, Silver Bay, South Toms River, and Windsor) were completed, these well fields were not considered to be potential exposure pathways in this study. Odds ratios for these other well fields fluctuated above and below 1.0 in both the Interview and Birth Records Study with little coherent pattern detected. Many of these other wells supplied small amounts of water to a limited number of study residences and no water to many study residences, and odds ratios often could not be calculated.

Exposure to Air Pollution from Point Sources

Ambient air exposure was evaluated for emission from the Ciba-Geigy facility and Oyster Creek Nuclear Generating Station. In the Interview Study high and medium prenatal exposure categories for Ciba-Geigy ambient air were elevated for females with leukemia diagnosed prior to age five (high exposure category OR=19; medium exposure category OR=5.2). Five of seven of the female leukemia cases under age five were in the medium or high Ciba-Geigy exposure categories while only nine of 27 controls were in those categories. When the medium and high Ciba-Geigy exposure categories were collapsed into a single exposure category, the new odds ratio for leukemia in females diagnosed prior to age five was elevated (OR=7.5) relative to the low exposed group. Similarly for the Birth Records Study, elevated odds ratios were found for the prenatal high and medium exposure categories of Ciba-Geigy ambient air exposure in females diagnosed prior to age five with leukemia (high exposure category OR=7.8; medium exposure category OR=2.0). The postnatal high category for Ciba-Geigy ambient air exposure was also elevated (OR=5.5) for females with leukemia, diagnosed prior to age five. These are consistent with the study's a priori hypothesis that air pollution from the Ciba-Geigy facility was a risk factor for childhood leukemia.

To examine the potential for confounding of the estimated odds ratio for the Ciba-Geigy ambient air prenatal exposure variable for female leukemia, adjusted odds ratios were calculated in relation to the time-specific Parkway well field water exposure, the Ciba-Geigy pipeline exposure variables, and the non-environmental factors for which associations with leukemia were observed. In general, after adjustment for these factors the odds ratio for the Ciba-Geigy ambient air exposure remained elevated.

Manufacturing operations at the Ciba-Geigy facility began in 1952 and ceased in 1996. Over the years, the facility produced anthraquinone-based dyes, azo dyes, epoxy resins, and other specialty chemicals. Ciba-Geigy was the only industrial facility in the Dover Township area which met the New Jersey Department of Environmental Protection's definition of a major emitter of hazardous air pollutants, which included carcinogenic materials. Very limited historic emissions data for the facility were available to adequately characterize potential exposure to the community. The modeled Ciba-Geigy estimates for ambient gaseous air pollution were closely correlated with modeled ambient particulate levels (see Volume IV, Appendix F) and are likely a surrogate of exposure to both gaseous and particulate air pollution arising from the site.

Exposure to Oyster Creek ambient air emissions did not appear to be associated with any childhood cancer groups evaluated in either the Interview or Birth Records Studies.

A British research group has reported that birth residences of children who died from cancer were geographically associated with a variety of industrial sites that emitted petroleum-derived volatile chemicals; furnace or kiln smoke and gases; or internal combustion engines (Knox and Gilman, 1997; Knox and Gilman, 1998).

Other Environmental Factors

Residential Proximity to Sites of Concern: Residence near select sites of concern was also evaluated for each child. In the Interview Study, the variable "ever

having lived within one-half mile of the Ciba-Geigy pipeline" was statistically elevated (during the total study time, prenatal, and postnatal periods) among females diagnosed with leukemia (ORs ranging between 5.1 and 17). However, when proximity to one of the four locations of known breaks in the pipeline after the breaks occurred was taken into consideration, few children were exposed and the odds ratios diminished. The other sites of concern did not display any pattern of consistency in the Interview Study. There was no pattern or consistency in the odds ratios for proximity to the pipeline or any other site of concern in the Birth Records Study. The index for proximity to the Ciba-Geigy pipeline was statistically correlated with the time-specific Parkway well field index in the Interview Study ($r=0.30$), but no correlation was found in the Birth Records Study. It is important to note that no known completed exposure pathway for the Ciba-Geigy pipeline has been identified (NJDHSS and ATSDR, 2001a). None of the exposures to other sites of concern appeared to be associated with any childhood cancer groups evaluated in either the Interview or Birth Records Studies.

Birth Residence Year of Construction: The age of birth residences (pre- and post-1970) was evaluated in the Birth Records Study. While this variable does not represent an a priori exposure pathway in this study or any particular environmental exposure, it was considered because of the results of a separate investigation by EOHSI that detected elevated cesium 137 levels in attic dust of older (pre-1970) houses in both Dover and non-Dover locations. EOHSI concluded that the elevated cesium 137 levels in older houses were primarily the result of above-ground nuclear weapons testing and global fallout that occurred in the 1950s and 1960s. While older birth residences did not appear to be associated with leukemia, the odds ratio for birth residences constructed pre-1970 and brain and central nervous system cancer was elevated fourfold in the Birth Records Study. An analysis of birth residence year of construction was unable to be completed for the Interview Study because of the lack of access to records with residential construction date.

Other Factors

The etiologic factors for childhood cancer are not well understood. Numerous studies have been conducted to evaluate a variety of factors which might be associated with an increased risk of childhood cancer. With the exception of a few factors that have been consistently identified in the literature, such as congenital disorders and certain prenatal exposures like ionizing radiation, there is little consistency for most other potential risk factors examined to date. (For a more detailed discussion on the literature of childhood cancers, see Volume IV, Appendix B.) In addition to the distinct environmental factors evaluated in this study, information on a wide variety of other factors was collected. These other factors were included because they have been traditionally evaluated in other studies, some studies have suggested the factor may be potentially causal, or the factor may be a potential confounder to the environmental factors of interest.

Parental Occupation: Information on parental occupation was only available in the Interview Study. An industrial hygienist (IH) rating was developed for categories of job activities and substance exposures for each child's parent. Few study mothers had any exposure to the job activities or substance categories. Study fathers appeared to have more occupational exposures than study mothers. Paternal exposure to dyes and pigments, petroleum products, ever having worked in chemical manufacturing, and ever having done electrical or electronics work were associated with several case groupings. Significantly elevated odds ratios were seen for paternal exposure to dyes or pigments, as well as for paternal work in chemical manufacturing, and appear to be due to three case fathers and one control father who reported prior employment at Ciba-Geigy. Maternal exposure to radiation (ionizing or low frequency) and ever having done electrical or electronics work were associated with brain and central nervous system cancers, and all cancers during the postnatal time period. The published literature suggests that the strongest occupational evidence of risk for childhood cancer appears to be for paternal exposure to solvents, chemicals, paints/ pigments, pesticides, petroleum products, or

paternal employment in motor vehicle-related occupations and maternal employment in personal services and textiles occupations (Colt and Blair, 1998; O'Leary et al., 1991; Savitz and Chen, 1990; and Arundel and Kinnier-Wilson, 1986).

Demographic, Pregnancy and Birth Characteristics: In the Birth Records Study, the odds ratio for birth weight of 4,000 grams or more was statistically elevated for leukemia in children diagnosed prior to age five (OR=5.7), but only slightly elevated for the same case group in the Interview Study (OR=2.8). Although the elevated odds ratios for high birth weight suggest an association between high birth weight and leukemia, especially in children diagnosed under age five, the published literature on birth weight and childhood cancer is contradictory with some studies reporting an association (Yeazel et al., 1997; Daling et al., 1984; Kaatsch et al., 1998; Westergaard et al., 1997; Emerson et al., 1991), while other studies have found no association (Eisenberg and Sorahan, 1987; Forsberg and Källén, 1990; Robison et al., 1987).

In the Birth Records Study, being the mother's first live birth was found to be inversely associated with all cancers combined and all other cancers combined. In the Interview Study, being the mother's first live birth did not show any clear association, though many of the odds ratios were decreased but not statistically significant. While an inverse association between childhood cancer incidence and being the mother's first live birth has been reported in the published literature (Westergaard et al., 1997; Shaw et al., 1984; Savitz and Ananth, 1994), other studies have not confirmed this association (McCredie et al., 1999; Emerson et al., 1991; Robison et al., 1987; Forsberg and Källén, 1990).

In the Birth Records Study, the results differ among cancer types for prenatal care utilization being a risk factor for childhood cancer. While having less than adequate prenatal care utilization was positively associated with leukemia (especially in children diagnosed prior to age five), it was inversely associated with nervous system cancers. Inadequate prenatal care utilization could be a socioeconomic status surrogate for poor access to health care in general.

In the Interview Study, parental education displayed different patterns by cancer type: odds ratios were higher for a lower educational level of the mother or father and leukemia; while elevated odds ratios were found for a higher educational level of the mother or father and nervous system cancers. The Birth Records Study also found elevated odds ratios for a lower educational level of the mother or father and leukemia in children diagnosed prior to age five. These findings contrast with some prior studies that have reported that children with higher socioeconomic status are at increased risk for leukemia (Chow et al., 1996).

In the Birth Records Study, any complications of pregnancy was significantly associated with nervous system cancers in children diagnosed prior to age five. However, the types of complications on the birth certificate varied and provided no clear insight into the meaning of these results.

Family Medical History: Previous studies have demonstrated that certain genetic syndromes or heritable factors may be an important risk factor for some types of childhood cancer (Pritchard-Jones, 1996). In addition, some studies have found increased occurrence of cancer in relatives of children with leukemia or brain cancer (Chow et al., 1996). In the Interview Study, neither family history of cancer nor a history of birth defects or inherited conditions showed any clear association with childhood cancer.

Health, Medical Conditions and Medical Procedures: In the Interview Study, use of antibiotics for ten days or more by the child was significantly associated with leukemia and nervous system cancers combined. This association may be due to the necessity of the child taking antibiotics to treat diseases that are directly or indirectly related to the cancer. One previous study has reported an association between two specific antibiotics, chloramphenicol and syntomycin, and childhood leukemia (Shu et al., 1988).

A child's exposure to diagnostic x-rays was significantly associated with children diagnosed prior to age five with leukemia and nervous system cancers combined, and with nervous system cancers alone. The literature indicates that x-ray

exposure during pregnancy or radiation therapy during childhood can cause childhood cancer (Ries et al., 1999; Little, 1999; Zahm and Devesa, 1995). However, exposure to diagnostic x-rays could be reflective of the use of x-rays to evaluate conditions directly or indirectly related to the cancer prior to its actual diagnosis. When this variable was reevaluated with x-rays occurring within one year of a child's diagnosis removed from the analysis, the resulting odds ratios were substantially lower and not statistically significant.

Dietary Factors: Mother's use of multivitamin supplements during pregnancy was found to be inversely associated with leukemia and nervous system cancers combined and leukemia alone. Furthermore, all odds ratios were below 1.0 for prenatal maternal multivitamin supplementation. Published studies of childhood brain cancer have reported a potential "protective effect" for multivitamin usage (Preston-Martin et al., 1998; Bunin et al., 1993).

Many of the dietary cured meat variables (hot dogs; bacon, ham, or sausage; lunch meat; and cured meat) were inversely associated with cancer incidence. Consumption of cured or processed meats by the child or by the mother during pregnancy has been associated in some studies, but not in others, with increased risk of childhood brain cancer or leukemia (Blot et al., 1999; Preston-Martin et al., 1996c; Peters et al., 1994; Sarasua and Savitz, 1994; Bunin et al., 1993; Kuijten et al., 1990; McCredie et al., 1994). These inconsistencies may be a result of confounding by other variables, or differential recall between case and control families. While dietary recall by parents in case-control studies has been suggested to vary with the child's disease status (Wilkins and Bunn, 1997), a comparison of long-term dietary recall in adult cancer cases and a comparison population found that no marked differences in the ability to recall past diet overall, though some recall differences were noted by cancer grouping (Wilkens et al., 1992).

Prenatal consumption of greater than four glasses of tap water or drinks made from tap water per day was significantly associated with leukemia. However, odds ratios for water consumption were generally mixed by cancer type and age group,

with some elevated and some decreased. It should be noted that this variable includes water consumption at all residences (in and outside of Dover Township). The importance of the variable tap water consumption was its evaluation in the drinking water assessments discussed previously.

Exposure to Tobacco Smoke and Alcohol: Some studies suggest that parental smoking increases the risk of leukemia in children, but the evidence is mixed and inconclusive (Little, 1999; Kaatsch et al., 1998; Ji et al., 1997; Shu et al.,1996; Klebanoff et al., 1996; Zahm and Devesa, 1995). In this study, exposure to tobacco smoke, either prenatally or postnatally, was not associated with cancer incidence. Maternal alcohol consumption during pregnancy was also not associated with cancer incidence. In the Birth Records Study, maternal smoking and alcohol consumption during pregnancy were not evaluated since these data were not collected until late in the study period (1989 onward).

Household-Related Exposures: Chemicals, Animals and Electro-Magnetic Fields (EMFs): Both prenatal and postnatal self-reported regular use of an electric blanket, electric mattress pad, or heated water bed (household appliance EMF exposure) showed little consistency in the odds ratios. Although a child's regular use of these appliances was significantly associated with leukemia, usage of these items was infrequent in the study population. Some scientists suggest that exposure to household appliance EMFs can cause childhood leukemia or brain cancer while others argue that the data are still inconclusive (Hatch et al., 1998; Savitz et al., 1990; London et al., 1991; Preston-Martin et al., 1996a; Gurney et al., 1996).

CONCLUSIONS

As the final part of the investigation of the incidence of childhood cancer in Dover Township, Ocean County, the New Jersey Department of Health and Senior Services (NJDHSS) and the federal Agency for Toxic Substances and Disease Registry (ATSDR) conducted an epidemiologic case-control study to evaluate distinctive environmental exposure pathways identified in this community during earlier phases of the Public Health Response Plan: Parkway water exposure; Holly Street water exposure; contaminated private well water exposure; and Ciba-Geigy air emissions exposure. Association of selected childhood cancers with these environmental factors represent the study's primary hypotheses.

The results in this Final Report should be interpreted carefully and in conjunction with existing biological and epidemiologic knowledge. Due to the relatively small number of study subjects, the analyses are sensitive to random fluctuations in numbers, which can result in substantial imprecision in the odds ratios (reflected by wide confidence intervals). Based on a combination of evaluation criteria for determination of risk factor and cancer causal associations, NJDHSS and ATSDR have concluded the following:

* Several environmental factors of primary interest were found to be associated with leukemia in female children, specifically for the prenatal exposure time period. These associations were not found in male children.

* No environmental factor of primary interest appeared to be associated with brain and central nervous system cancer in either males or females.

* No consistent patterns of association were seen between the environmental factors of primary interest and any of the cancer groupings during the postnatal exposure period.

* Although no associations were detected in analyses of the overall study population, a statistically significant association and consistency in multiple

measures of association were seen between prenatal exposure to time-specific Parkway well field water (1982-1996) and leukemia in female children of all ages. This finding seems to support the hypothesis that prenatal exposure to Parkway well field water during this interval was a risk factor for childhood leukemia in females. However, it is important to note that there is considerable uncertainty in the findings.

* Although no associations were detected in analyses of the overall study population, a consistent elevation in the odds ratios and an apparent dose response effect was seen in both the Interview and Birth Records Studies between prenatal exposure to Ciba-Geigy ambient air and leukemia in female children diagnosed prior to age five. This finding seems to support the hypothesis that exposure to Ciba-Geigy air emissions was a risk factor for childhood leukemia in females. As noted above, there is considerable uncertainty in the findings.

* No associations were seen between exposure to Holly Street well field water prior to 1976 and any of the cancer groupings evaluated. However, because few children had any study time before 1976, the ability to examine this factor was limited in this study.

* The use of a private well for drinking water within any region that had a history of groundwater contamination was rare in this study. Odds ratios for leukemia were elevated in the Interview Study for ever living in a residence with a private well in any of these groundwater regions during the postnatal time period, but could not be calculated for the prenatal period.

* An association was observed during the prenatal and postnatal time periods for residential distance from the Ciba-Geigy pipeline and leukemia in female children, but the association diminished when documented Ciba-Geigy pipeline breaks were taken into consideration. No completed exposure pathways associated with the Ciba-Geigy pipeline were identified in the Ciba-Geigy Public Health Assessment.

* No consistent patterns of association were seen between the other environmental factors and any of the cancer groupings evaluated.

* Study findings related to the other factors evaluated were found to be generally consistent with the published literature, with the exception of the consumption of cured meat variables.

* The ability to adjust for confounding in this study was limited due to the limited number of study subjects.

RECOMMENDATIONS

1. The NJDHSS should update the *Childhood Cancer Incidence Health Consultation* when an additional five years of cancer incidence data (1996-2000) are available from the New Jersey State Cancer Registry in order to determine if there are any changes in childhood cancer incidence rates or time trends in Dover Township.

2. Efforts should be continued to cease or reduce exposure to hazardous substances, including:

    <   The effort to ensure that the Reich Farm groundwater pollution does not cause contamination of additional Parkway well field wells should be continued in order to guarantee that this exposure pathway is not completed. Periodic groundwater sampling of the Reich Farm plume should continue in order to ensure that the plume is accurately delineated and does not affect currently unaffected public supply wells. In addition, monitoring of the effectiveness of treatment systems now in place is necessary to ensure that contaminants are not reintroduced into the community water distribution system.

    <   All private well restriction zones in Dover Township should be maintained in order to ensure that this potential exposure pathway is not completed.

    <   Continued efforts should be made by the United States Environmental Protection Agency and Ciba Specialty Chemicals to contain and remove contaminants in the affected aquifer associated with the Ciba-Geigy site. The restrictions on the use and construction of private wells in areas known to be affected by the Ciba-Geigy site should be maintained. The remediation of the Ciba-Geigy property should continue in order to reduce the threat of further contamination of groundwater and prevent future exposures to hazardous chemicals.

3. Because of the complexity of issues in Dover Township, it would be beneficial to continue educational efforts on cancer, such as providing study-specific information and environmental health information to teachers and children in the schools, to health care providers, and to the community at large.

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