The Wilmington Childhood Cancer Study

An Epidemiologic Investigation of Childhood Cancer from 1990-2000

MARCH 2021

ACKNOWLEDGEMENTS

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EXECUTIVE SUMMARY

STUDY HIGHLIGHTS

- Elevated rates and an unusual pattern of childhood cancer in the town of Wilmington during the 1990s led to the undertaking of a broad environmental case-control study by the Massachusetts Department of Public Health (DPH).
- DPH interviewed each study participant and matched control to collect detailed information on residential history and major cancer risk factors including maternal health behaviors; family and child medical histories; and occupational or household exposures such as pesticides and solvents.
- In 2003, a carcinogenic compound, n-nitrosodimethlyamine (NDMA), was found in the groundwater supplying part of the town's public drinking water. This discovery prompted a comprehensive water modeling effort to reconstruct historical concentrations of NDMA at the residences of each study participant for each month between 1974 and 2000. An additional carcinogenic contaminant, trichloroethylene (TCE), was also present in the water supply during part of the study period and the report details analyses related to both compounds.
- Despite limitations, including a small sample size and modeled exposure estimates, study results show an association between childhood cancer and prenatal exposure to NDMA, or NDMA and TCE. This association is observed consistently in a series of analyses and the results are statistically significant with respect to the subset of leukemia or lymphoma diagnoses. These associations exhibit a dose-response trend in which higher estimated exposures result in higher odds of cancer and the associations remained positive even after adjustment for other known risk factors.
- Childhood cancer incidence returned to expected rates beginning in 2001.

BACKGROUND

The Massachusetts Department of Public Health (MDPH) was asked to investigate a suspected cluster of childhood cancer in Wilmington, MA. Local residents and the local board of health were concerned about what appeared to be an unusual number of childhood cancer cases during the 1990s. After a review of cancer incidence data for the years in question, the MDPH confirmed the presence of an unusual pattern of cancer among children and adolescents (aged ≤ 19 years) within two census tracts located in the southern and western portions of the town. Consequently, the MDPH initiated an epidemiologic case-control study to investigate factors that may be associated with cancer development in the town of Wilmington among children and adolescents diagnosed between 1990 and 2000.

Shortly after initiation of the study, a specific drinking water contaminant and carcinogen, n-nitrosodimethylamine (NDMA), was detected in an aquifer providing part of the Wilmington drinking water supply. The contamination occurred as a result of activities at a chemical manufacturing facility operating in the south- eastern corner of town from 1953–1986. The site, known as the Olin Chemical site, was later designated a Superfund National Priorities List site by the US Environmental Protection Agency. Potential exposure to NDMA and to another carcinogenic drinking water contaminant known to have been present in the Wilmington public drinking water distribution system in the 1970s and 1980s, trichloroethylene (TCE), became the focus of this investigation.

METHODS

Cases of childhood and adolescent cancer occurring in Wilmington, MA, during the period of concern were identified through the MDPH Massachusetts Cancer Registry and through Massachusetts hospital discharge records. Eligible cases were those diagnosed with a first primary cancer prior to their 20th birthday, with a diagnosis date between January 1, 1990 and December 31, 2000, and who were residents of Wilmington at the time of diagnosis. One case of melanoma that was otherwise eligible, was excluded since sunlight exposure is the major risk factor for that cancer type, making the case unlikely to be relevant to this environmental investigation.

Eighteen out of twenty-one eligible children and adolescents were enrolled in the study. In addition, seventy-four control children and adolescents (approximately four controls per case matched on age and sex) were enrolled in the study. Controls were randomly selected from public school rosters and Wilmington high school yearbooks and were required to have lived in Wilmington during the same month and year of their matched case's cancer diagnosis. The parents of all study participants completed a

comprehensive structured interview to collect residential histories as well as risk factor information such as maternal alcohol use, smoking status, and reproductive history; child/adolescent's medical history; child/adolescent's daycare, school, camp, and recreational history for specific locations in Wilmington; occupational history for each child or adolescent (if applicable) and parent; and potential household exposures such as pesticides and solvents.

Utilizing residential history information collected during participant interviews, MDPH estimated exposure to NDMA for the period 1974–2000 using sophisticated computer models to replicate historical groundwater flow, transport of NDMA through the groundwater, and distribution of NDMA throughout the Wilmington public drinking water system. TCE was modeled over the period 1981–2000. Modeling of TCE concentrations prior to 1981 was not possible due to the absence of earlier sampling data along with the lack of a known source within the aquifer. Each contaminant was evaluated for an association with the odds of childhood/ adolescent cancer based on exposure during two etiologic periods: the maternal exposure period defined as the year prior to the child/adolescent's birth (representing *in-utero* exposure) and the childhood exposure period encompassing all of childhood/ adolescence from the month of birth to the date of diagnosis for each case and their matched control.

Modeled concentrations of NDMA and TCE in the water at each residential address were used as a surrogate for potential exposure. The estimated average of all non-zero monthly concentrations of NDMA was used as the measure of exposure to NDMA. The estimated average of all non-zero monthly concentrations of TCE was used as the measure of exposure to TCE. Analyses of NDMA and TCE exposure were conducted as dichotomous (ever/never) and as categorical (zero/low/high) where the division between low and high was based on the median average non-zero monthly concentration. Participants were asked about their primary drinking water source for each residence and analyses were also conducted to evaluate potential exposure while accounting for bottled water usage during the maternal exposure period.

Analyses of risk factors were conducted among all study participants combined (the All Cancers group) and separately for those diagnosed only with leukemia or lymphoma and their matched controls (the Leukemia/Lymphoma subgroup). The leukemia and lymphoma cases were analyzed together because there is some evidence that these cancer types may share a more similar etiology compared to all types of cancer combined.

RESULTS

Exposure Concentrations

For NDMA exposure in the All Cancers group, fifty percent (50%) of case mothers are estimated to have had NDMA present in their tap water during at least one month in the year prior to their child's birth compared to 34% of control mothers. The median non-zero monthly concentration estimated at the tap of case mothers is 52.2 ng/L compared to 46.8 ng/L for control mothers. The likelihood of having had any NDMA in residential tap water during childhood was similar for cases and controls (78% vs. 84%). Estimated median non-zero concentrations during the childhood period were also higher for cases compared to controls (51 ng/L versus 39 ng/L). Similar results are seen in the Leukemia/Lymphoma subgroup for both maternal and childhood NDMA exposure.

For TCE exposure in the All Cancers group, mothers of cases were slightly more likely to have had any TCE in their residential tap water compared to mothers of controls (31% compared to 25%), but median concentrations were similar between the two groups. The inverse is true for the childhood exposure period with controls being slightly more likely to have had at least one month with TCE estimated to be present in their tap water (53% of controls compared to 46% of cases). However, estimated median non-zero concentrations during the childhood period were approximately twice as high for cases compared to controls (5.2 µg/L versus 2.1 µg/L). Similar results are seen in the Leukemia/Lymphoma subgroup for both maternal and childhood NDMA exposure.

When joint exposures were evaluated for the maternal exposure period, it was observed that no participants were exposed to TCE alone and that 31% of cases and 25% of controls were estimated to have been exposed to both contaminants (among the 73 participants with modeled concentrations of both NDMA and TCE). A small, but statistically significant, correlation exists between the two contaminants in residential drinking water in this study, driven by the large number of participants with estimated zero exposure to both compounds.

Associations between NDMA in Drinking Water and Childhood Cancer

When evaluating maternal/in-utero exposure, the odds of childhood/adolescent cancer (all cancers and leukemia/lymphoma only) were higher for children/adolescents whose mothers ever lived in a home estimated to have NDMA-contaminated drinking water during the year prior to birth, but these results did not reach statistical significance. A positive trend in the odds of cancer was also observed with increasing average estimated NDMA concentrations in maternal drinking water from zero to low to high for all cancers (ORs = 1.0, 1.3, 3.0) and for leukemia/lymphoma (ORs = 1.0, 1.3, 5.0). Tests of trend for these analyses resulted in a p-value of 0.12 for the All Cancers analysis and a p-value of 0.06 for the Leukemia/Lymphoma subgroup analysis. In the Leukemia/Lymphoma sub-analysis, the odds ratio of 5.0 was statistically significant for the high concentration group compared to the zero exposure group. The odds ratio of 3.0 for the high category of the All Cancers analysis was of marginal statistical significance (p = 0.09).

> An **odds ratio (OR)** is a measure of association between a health outcome and an exposure or risk factor. In general, an odds ratio is calculated as the odds of an exposed population developing a particular health outcome compared to the odds of an equivalent but *un*exposed population developing the health outcome.
>
> - An OR of 1.0 means that exposure is not related to the outcome.
> - An OR greater than 1.0 means that exposure has a positive association with the outcome.
> - An OR less than 1.0 means exposure has a negative association with the outcome.
>
> *Example: An odds ratio of 2.5 means that the odds of an outcome occurring with exposure is 2.5 times higher than if there were no exposure.*

In contrast to the results for maternal NDMA concentrations in drinking water, when evaluating concentrations estimated to have been present in residential drinking water during childhood/adolescence, there was no evidence of a positive association between NDMA in drinking water with development of any cancer, including development of leukemia or lymphoma.

Associations between TCE in Drinking Water and Childhood Cancer

When evaluating maternal exposure to TCE, the odds of childhood/adolescent cancer (all cancers and leukemia/lymphoma only) were higher for children/adolescents whose mothers ever lived in a home estimated to have TCE-contaminated drinking water during the year prior to birth, but these results do not reach statistical significance and the confidence intervals are very wide. A similar result was observed in the Leukemia/Lymphoma subgroup analysis. When evaluating childhood/adolescent TCE concentration estimates, there was no evidence of a positive association with development of cancer.

Other Considerations

When those reporting that they primarily drank bottled water were assigned zero exposure, associations between NDMA and childhood/adolescent cancer were no longer observed. However, when bottled water usage was accounted for in exposure assignments by decreasing estimated concentrations to 49% of modeled values, associations between NDMA and childhood/adolescent cancer were strengthened (though no longer in a dose-responsive fashion).

For TCE, accounting for bottled water usage had less of an apparent effect. The effect of possible confounding on the associations between childhood/adolescent cancer and exposure to NDMA and TCE was evaluated for each of eleven individual covariates: 1) oxygen given after birth, 2) incubator use after birth, 3) low birth weight, 4) adverse birth event, 5) prenatal ultrasound, 6) antihistamine use by the child/adolescent, 7) metals, alloys, or solder exposure, 8) plastics, synthetics, or resins exposure, 9) exhaust fume exposure, 10) herbicide exposure, and 11) maternal occupational exposure to ionizing radiation. These variables were selected for evaluation because they were found to have elevated odds ratios and p-values that were <0.20 for the association with all cancers or with leukemia/lymphoma, meaning that they had a reasonable potential to be confounders in the main exposure-outcome evaluation. In all adjusted models, potential exposure to NDMA and to TCE in maternal drinking water remained positively associated with childhood and adolescent cancer.

Confidence Intervals, *p*-Values, and Statistical Significance

While an odds ratio (OR) provides a point estimate of the association between a risk factor and a health outcome, other tools are used to understand the reliability or precision of that estimate.

A **confidence interval (CI)** measures how precise the odds ratio is and provides a range of values within which the point estimate will fall 95% of the time given an unbiased sample and analysis. A CI that includes 1.0 means that the association is not statistically significant and may be due to chance, even if the OR estimate is much higher than 1.0. If the CI excludes 1.0, then the association can be considered statistically significant. A wide confidence interval that excludes 1.0 indicates that the association is statistically significant, but that the precise strength of the association is not clear.

A ***p*-value** is a related measure, which describes the statistical significance of an odds ratio or other effect estimate based on a pre-defined confidence threshold. A threshold of 0.05 (or 95% confidence) is generally applied. The larger a p-value, the less precise the OR is. However, importantly, a large p-value does not mean that the result is invalid. It may indicate that insufficient information is available to adequately evaluate the result, commonly due to small sample sizes.

DISCUSSION

The objective of this study was to obtain an explanation for the pattern of childhood cancer in Wilmington, MA between 1990 and 2000. Specifically, childhood/adolescent cancer rates were higher than would be expected and appeared to occur more frequently in certain areas of the town. The study was maximally designed to consider available risk factor data, given the relatively small number (from a statistical perspective) of children and adolescents with cancer, by using multiple controls, sophisticated exposure modeling, and detailed personal interviews. This study faced several challenges including a small sample size, a retrospective exposure assessment, and a retrospective ascertainment of additional risk factors. Nevertheless, strong positive associations were observed between contaminants in maternal residential drinking water and childhood/adolescent cancer.

The most compelling results include statistically significantly higher odds of a leukemia or lymphoma diagnosis among children or adolescents whose mothers lived in homes with the highest estimated n-nitrosodimethylamine (NDMA) concentrations in drinking water compared to children or adolescents whose mothers were estimated to have had no NDMA exposure during the year before their child's birth (OR = 5.0; 95% CI: 1.0-24). The odds of any cancer diagnosis were also elevated among this group, but with only marginal statistical significance (OR = 3.0; 95% CI: 0.8-11); because leukemia and lymphoma diagnoses made up 60% of the 18 cases in this study, the results of the All Cancers analysis are largely driven by the strong association observed with leukemia/lymphoma. Both associations displayed a dose-response trend, and the trend for the Leukemia/Lymphoma subgroup had a marginally significant p-value of 0.06. Estimated concentrations of trichloroethylene (TCE) in maternal drinking water were also positively associated with the odds of any cancer diagnosis, but results were not statistically significant, a dose-response effect was not observed, and the small number of participants with available estimated TCE concentrations prevented deeper analysis of the Leukemia/Lymphoma subgroup.

Assessing the effects of each contaminant in a multivariate model, while not wholly appropriate due to their correlated nature, nevertheless resulted in continued positive associations with childhood/adolescent cancer for both the All Cancers group and the Leukemia/Lymphoma subgroup. Such results may suggest independent associations of each contaminant with childhood/adolescent cancer in this population; however, the lack of a sample only exposed to TCE and the very small number of those only exposed to NDMA severely limits the ability to evaluate independent effects.

There is ample evidence in the published literature on the plausibility of NDMA causing cancer and it is considered a probable human carcinogen by both the US EPA and the

International Agency for Research on Cancer (IARC) (IARC 1978, 1987; US EPA 2017). In animal studies, NDMA has been shown to be a transplacental carcinogen (CalEPA 2006), meaning that it can cross the placenta and cause cancer in the animal's offspring. For TCE, the US Department of Health and Human Services, US EPA, and the IARC have all determined it to be a human carcinogen (ATSDR 2019; Guha et al. 2012; IARC 2014; NTP 2011; US EPA 2011). Epidemiological studies provide strong evidence that TCE can cause kidney cancer in humans and some evidence that it causes non-Hodgkin lymphoma and liver cancer. While most studies evaluate adult worker populations, children are expected to have similar health effects as adults (ATSDR 2019).

Although this study's risk estimates were not precise, the associations suggested with past NDMA and/or TCE drinking water exposures offer what we believe is a plausible explanation, supported by valid objective data, for the pattern of elevated cancer observed in areas of Wilmington, MA. The presence of these contaminants cannot definitively explain the pattern of childhood/adolescent cancer, but it should be recognized that despite the low statistical power of the study, several findings reported here do reach the traditional threshold of statistical significance, are plausibly supported by the literature, and could be real. However, as in any study, the statistical associations found could have been affected by bias or confounding or could be due to chance.

Criteria Used To Draw Study Conclusions

Statistical significance was used in this study as a tool to help identify potentially meaningful results. However, statistical significance was not the only criteria used to interpret results and draw conclusions; results that are not statistically significant may still be considered relevant. Careful consideration of the following contributed to all study conclusions:

- The magnitude of ORs
- The width of CIs
- *P*-values
- The presence or absence of dose-response trends
- The presence of consistency in the results
- The plausibility of an association based on the scientific literature
- The presence and potential impact of any confounding, measurement error, or bias.

CONCLUSIONS

Despite a number of limitations including a small sample size, an exposure assessment based on limited historical data of NDMA and TCE in the town's drinking water, and an inability to account for dietary NDMA exposure, the study was able to reach several important conclusions:

1. Comprehensive information on NDMA in groundwater and the historical Wilmington water distribution system enabled development of a computer model to predict the movement of NDMA to public water supply wells and in the water distribution system, enabling estimation of monthly NDMA concentrations at each study participant's residence between 1974 and 2000;

2. Detailed interviews of each participant and matched control provided information on major risk factors known or suspected from the published scientific literature for the types of cancer diagnosed among the Wilmington children and adolescents;

3. An association between maternal exposure to NDMA during the year before the child's birth and risk of that child developing cancer was strongly suggested by the results of this study. This association was statistically significant for the Leukemia/Lymphoma subgroup, marginally significant for the All Cancers group, and a dose-response effect was observed. We cannot rule out that this finding was confounded by exposure to TCE, but the effect is plausibly supported by the literature and could be a real one;

4. A positive association between maternal exposure to TCE during the year before the child's birth and risk of that child developing cancer was not statistically significant and a dose-response effect was not observed, meaning that we cannot rule out the possibility that the finding is due to chance, although it must also be recognized that the study was necessarily underpowered due to a small population and that the association is plausibly supported by the literature. It should also be noted that it is impossible to evaluate the effect of TCE alone using the data available;

5. Minimal evidence for an association between childhood/adolescent cancer and exposure to NDMA during childhood/adolescence was observed;

6. A statistically significant increased risk of cancer was observed among a small number of cases who were treated with oxygen immediately following birth, among a small number of cases born with low birth weight, and among all cases having any one of three reported adverse birth events (oxygen at birth, low birth weight, or incubation).

INTRODUCTION

In the spring of 1999, residents of the town of Wilmington, State Representative James Miceli, and the Wilmington Board of Health (BOH) asked the Massachusetts Department of Public Health's (MDPH) Bureau of Environmental Health (BEH) to investigate a suspected cluster of childhood cancer (Wilmington BOH 1999). Of primary concern was the number of Wilmington children diagnosed with brain cancer, Hodgkin disease, leukemia, and non-Hodgkin lymphoma between 1990 and 1999 residing in the Kelly Hill section of town and the possibility of an association with environmental factors. Residents suggested a number of possible environmental exposures, including drinking water contamination, illegal dumping suspected at several businesses, and hazardous waste sites located throughout the town. The MDPH's initial investigation involved a review of childhood cancer incidence data for the years 1987-1995, the latest year for which complete cancer statistics were available at the time (MDPH 2000). That investigation identified an unusual pattern of children with cancer residing within census tracts 3312 and 3313, which are located on the west side of Wilmington (see Map of Wilmington in

Figure 1). Subsequently, the legislature provided funding to conduct an epidemiologic study of childhood cancer in Wilmington, the findings of which are presented in this report. The study protocol was approved by the MDPH Institutional Review Board in November 2001 and the case-control study began in 2002.

The objective of this study was to investigate environmental and other factors that may be associated with childhood cancer development in the town of Wilmington among children and adolescents diagnosed between 1990 and 2000. Hereinafter, "children" refers to children and adolescents 19 years of age or younger. The families of children diagnosed with childhood cancer and their matched controls (i.e. children of the same age and sex not diagnosed with cancer) were asked to participate and be interviewed for the study. The interviews were used to collect information about childhood cancer risk factors that each child may have experienced, to obtain residential histories, and to identify potential environmental factors that might help explain the unusual pattern of childhood cancer observed.

In 2003, a specific drinking water contaminant and carcinogen called *n*-nitrosodimethylamine (NDMA) was detected in an aquifer providing part of the Wilmington drinking water supply. For this reason, public drinking water supply wells found to be contaminated were shut down at that time. The contamination occurred as a result of activities at a chemical manufacturing facility operating in the southeastern corner of town from 1953-1986. The US Environmental Protection Agency (EPA) later

added the facility to the Superfund National Priorities List (NPL) in 2006 as the Olin Chemical site, named for the property owner at the time of listing (US EPA 2019).

Figure 1. Map of Wilmington, MA
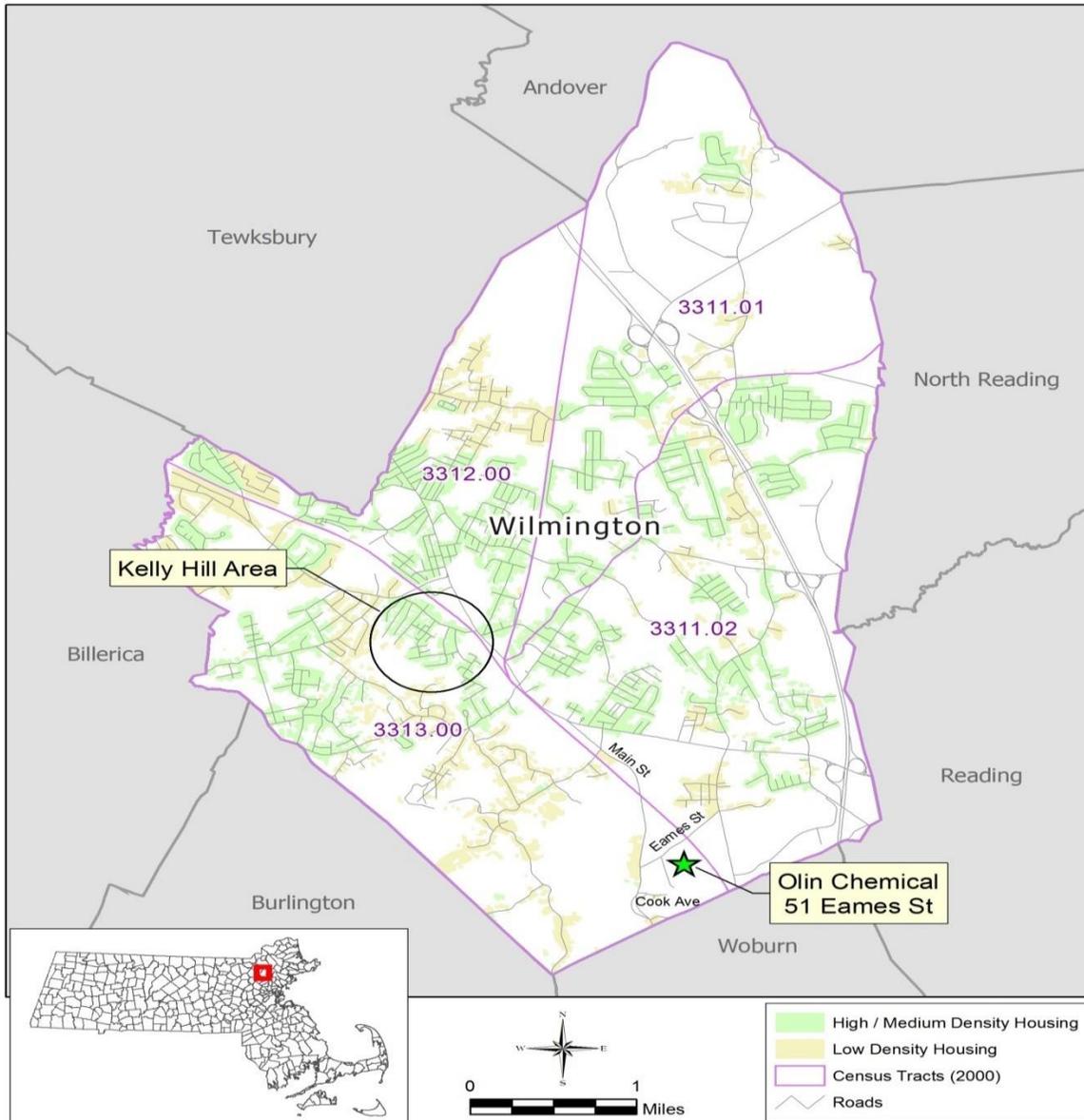
With the detection of NDMA contamination, residents (and, notably, families of children diagnosed with cancer) and the Wilmington BOH asked MDPH to postpone analysis until better information related to water contamination was available (MDPH 2004). Utilizing residential history information collected during interviews with study participants, MDPH estimated exposure to NDMA for the period 1974-2000 using sophisticated computer models to replicate historical groundwater flow, transport of NDMA through the groundwater, and distribution of NDMA throughout the Wilmington public drinking water system. Trichloroethylene (TCE), another contaminant in the public drinking water system, but with different (and unknown) sources, was modeled over the period (1981-2000). Modeling of TCE concentrations prior to 1981 was not possible due to the absence of earlier sampling data along with the lack of a known source within the aquifer. The exposure assessment took place over three phases from 2006 to 2013, as funding allowed and as new information relevant to understanding of the contamination surfaced.

Information was collected on a multitude of risk factors for childhood cancer, including estimated exposure to NDMA and TCE. Each was evaluated for an association with the odds of childhood cancer among the study population. This report presents the methods used in the investigation and its results and conclusions.

GOALS AND OBJECTIVES

The goal of the Wilmington Childhood Cancer Study (WCCS) was to evaluate factors that may help to explain the pattern of cancer among children in Wilmington, Massachusetts; specifically to determine if drinking water reported to be contaminated with a carcinogen called *n*-nitrosodimethylamine (NDMA) was associated with childhood cancer in Wilmington. Another contaminant and carcinogen in Wilmington's drinking water, trichloroethylene (TCE), and its association with childhood cancer was also investigated.

The specific objectives were:

1. Determine all cases of childhood cancer from 1987-2000 among Wilmington residents ages 0-19 at time of diagnosis;
2. Select multiple controls from Wilmington school rosters and match to each case so that age and sex were similar;
3. Conduct personal interviews of families of all children diagnosed with cancer and a control group to evaluate possible environmental and other risk factors for cancer;
4. Estimate potential exposure of study participants to NDMA as residents of Wilmington during the period 1974 to 2000 based on historical drinking water simulations and

residential histories of mothers during gestation and of children from birth to date of diagnosis; and to TCE during the period of 1981 to 2000; and

5. Identify any associations between possible risk factors and childhood cancer in Wilmington, including the likelihood of an association between childhood cancer and exposure to NDMA or TCE in municipal drinking water.

To meet these objectives, the following tasks were implemented:

1. Cases and matched controls were recruited for participation in the study;
2. Community input was sought and obtained on the information to be collected;
3. A pilot-tested survey instrument was used to collect important background information including residential and occupational histories;
4. Environmental information pertaining to the municipal drinking water system, including data on groundwater and the Olin Chemical site, was reviewed with the US EPA, the Massachusetts Department of Environmental Protection (MA DEP), and the Wilmington Water and Sewer Division to ensure that the most up-to-date data were incorporated into the groundwater and water distribution system models;
5. The potential for exposure to NDMA was estimated by: (a) Developing a groundwater flow and contaminant fate and transport model to determine when and at what concentration NDMA would be transported through groundwater to municipal drinking water wells and (b) Developing a drinking water distribution system model to estimate average monthly concentrations of NDMA at each residence on public water for each month between 1974 and 2000;
6. The potential for exposure to TCE was established by estimating average monthly concentrations of TCE for each residence on public water for each month between 1981 and 2000 utilizing historical drinking water distribution system sampling data and the drinking water distribution system model;
7. Associations between the probability of being diagnosed with childhood cancer and risk factors such as maternal smoking and medical radiation were estimated using univariate statistical methods.
8. Associations between the probability of being diagnosed with childhood cancer and estimated concentrations of NDMA and TCE in residential drinking water were analyzed using univariate and multivariate statistical analyses taking into consideration the effects of possible confounding factors.

BACKGROUND

OVERVIEW AND STUDY TIMELINE

The town of Wilmington, Massachusetts is located approximately 17 miles northwest of Boston. Its population in 1970, near the beginning of the study period, was 17,102; by 2000, the population had grown modestly to 21,363 (US Census 1973; US Census 2002). The percent of the population that was 19 years old or younger was 46% in 1970 and 29% in 2000 (US Census 1973; US Census 2002). Wilmington is a suburban community with a mix of residential neighborhoods, commercial districts, and industrial parks. In 1971 and 1999, residential land use made up about 27% and 35% of the town, respectively, whereas commercial/industrial land use made up about 6% and 11% of the town (MassGIS 2003). At least 95% of residences received drinking water from the Wilmington public water system throughout the study period (US Census 1972).

Figure 1 shows the location of Wilmington within Massachusetts and the town census tract boundaries. Of specific interest are the locations of the Olin Chemical site and the Kelly Hill neighborhood, both in census tract 3313 and of particular focus in this investigation.

In March of 1999, Wilmington residents, State Representative James Miceli, and the Wilmington Board of Health (BOH) each contacted the Massachusetts Department of Public Health (MDPH) Bureau of Environmental Health (BEH) requesting an investigation of a suspected cluster of childhood cancer for a period beginning in 1990 (Wilmington BOH 1999). Initial interest was in leukemia but concerns were also raised about other childhood cancers including bone cancer, brain cancer, and Hodgkin and Non-Hodgkin lymphoma. Residents reported the suspected clustering of cases in the Kelly Hill neighborhood of census tract 3313

> ### Standardized Incidence Ratio (SIR)
>
> An SIR demonstrates whether the number of observed cancer cases in a particular geographic area is higher or lower than expected, based on the statewide experience and given the population and age distribution for that community. An SIR greater than 100 indicates that more cancer diagnoses occurred than were expected. Confidence intervals and statistical significance are also typically evaluated to help understand the statistical precision of an SIR. A confidence interval that includes 100 indicates that the difference between observed and expected numbers of cases is not statistically significant and may be due to chance. When fewer than five diagnoses are present, the SIR is not statistically reliable and is, therefore, not calculated.

Figure 1). MDPH, therefore, conducted a preliminary evaluation of childhood cancer incidence in Wilmington, MA (MDPH 2000).

The MDPH Massachusetts Cancer Registry (MCR) provided information on all cases of childhood cancer reported for Wilmington children from 1987 through 1995, the latest year for which the MCR contained complete data. Records at the time identified 11 Wilmington children (≤ 19 years old) that had been diagnosed with some type of cancer during the 1987-1995 period and that 8 of the cases were male. The MCR later found during routine quality control activities that one female case was incorrectly included so the correct case count for that time period was actually 10.

Table 1. presents the observed and expected number of total childhood cancer cases estimated for each census tract and for the town as a whole along with Standardized Incidence Ratios (SIRs) during for the period 1987-1995. As seen in Table 1., more children were diagnosed with cancer during this period than expected, with the excess cases being driven by incidence among males. Female childhood cancer incidence was not elevated. The town SIR for males and females combined is 130, and the SIR for males alone is 187. Though neither SIR is statistically significant, it was also observed that the majority of cases were among children in census tracts 3312 and 3313. Small numbers limited the calculation of SIRs at the census tract level, but the elevated town-level SIRs and the geographic pattern of cases prompted the MDPH to conduct a full-scale case-control epidemiologic study.

Table 1. Childhood Cancer Incidence in Wilmington, MA, 1987-1995

All Childhood Cancers									
Census Tract	Total			Males			Females		
	Observed Cases	Expected Cases*	SIR	Observed Cases	Expected Cases*	SIR	Observed Cases	Expected Cases*	SIR
3311.01	1	0.8	NC	1	0.4	NC	0	0.2	NC
3311.02	2	2.3	NC	1	1.4	NC	1	0.9	NC
3312	3	2.3	NC	3	1.2	NC	0	1.1	NC
3313	4	2.2	NC	3	1.2	NC	1	1.0	NC
Town	10	7.7	130	8	4.3	187	2	3.4	NC

SIR = Standardized Incidence Ratio
NC = When fewer than five diagnoses are present, the SIR is not statistically reliable and is, therefore, not calculated.
*Numbers may not sum due to rounding
NOTE: After public release of these data in 2000, a correction of the Massachusetts Cancer Registry (MCR) database was made as part of standard quality control activities by hospitals and the MCR.

As a result, the total number of childhood cancer cases was updated from 11 to 10 and the number of females with a childhood cancer changed from 3 to 2 as is reflected in the table.

Formal initiation of the case-control study began in 2002 following preparation of a scientific protocol and approval by the MDPH Institutional Review Board. In that time, two additional years of cancer data (1996-1997) became available through the MCR and MDPH also sought out the most recently diagnosed cases (1998-2000) by directly contacting hospitals. As shown in Table 1., additional cases of cancer were diagnosed in Wilmington children over the next few years and an unusually high number were diagnosed in 1999 and 2000. Only two cases had been diagnosed between 1982 and 1989 (not shown), but 12 cases were diagnosed in the following eight-year period (1990-1997), and 11 more cases in the final three years of available data (1998-2000).

Figure 2. Childhood cancer cases diagnosed in Wilmington, MA, by year (1987-2000)
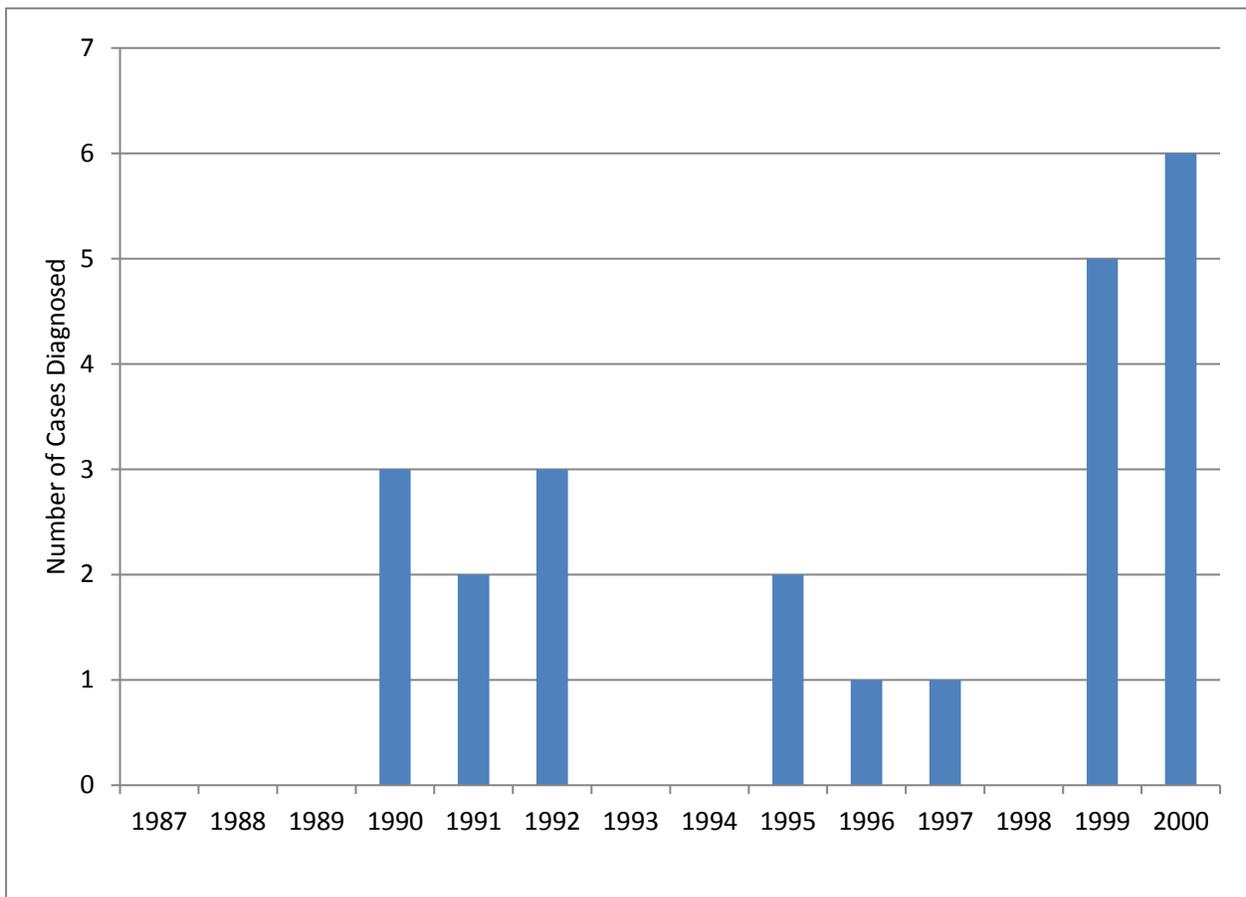
At the onset of the study, no specific environmental exposures or cancer risk factors were suspected in relation to the town's cancer incidence. MDPH and involved community members, therefore, considered the study to be exploratory with the hope of

identifying environmental or non-environmental factors common to the cases that could contribute to understanding the pattern of childhood cancers in Wilmington. Shortly after MDPH's plans to initiate the study, an environmental investigation by the US EPA identified concerns associated with a newly discovered contaminant in Wilmington drinking water, NDMA.

This discovery led to a refocus of the study on drinking water contamination (US EPA 2005) and, although interviews of cases and controls were completed in 2004, data analysis was postponed by mutual decision of the Wilmington Childhood Cancer Study Advisory Committee, the Wilmington BOH, and MDPH until a complete exposure assessment of NDMA in drinking water could be completed. While MDPH awaited results of environmental investigations by federal agencies, interview data were reviewed for quality assurance and quality control, data were coded, and an analytic database was created. In 2006, MDPH began working with engineering consultants to begin the exposure assessment phase of the study. Building on work completed by EPA and private contractors, historical modeling of NDMA concentrations in groundwater and in the Wilmington public drinking water distribution system was completed over three phases from 2006 to 2013, as funding allowed and as new information relevant to understanding of the contamination surfaced. Subsequent epidemiologic analysis was initially completed in 2014, followed by a first round of peer review. Additional exposure assessment work, including more in-depth evaluation of TCE exposure, was conducted from 2015-2017 (for more details, see the Peer Review section of Methods). Study analyses were completed in 2018 and a final peer review was conducted at the end of 2019.

As of the writing of this report, the most recent and complete year of childhood cancer incidence data available from the MCR was 2015. As shown in Figure 3. , the incidence of childhood cancer in Wilmington, MA from 2001 to 2015 varied from 0 to 2 cases per year. Over this period, the number of diagnoses each year was similar to what would be expected based on statewide data and the SIR for the entire 15-year period was 72.

Figure 3. Childhood cancer cases diagnosed in Wilmington, MA, by year (2001-2015)
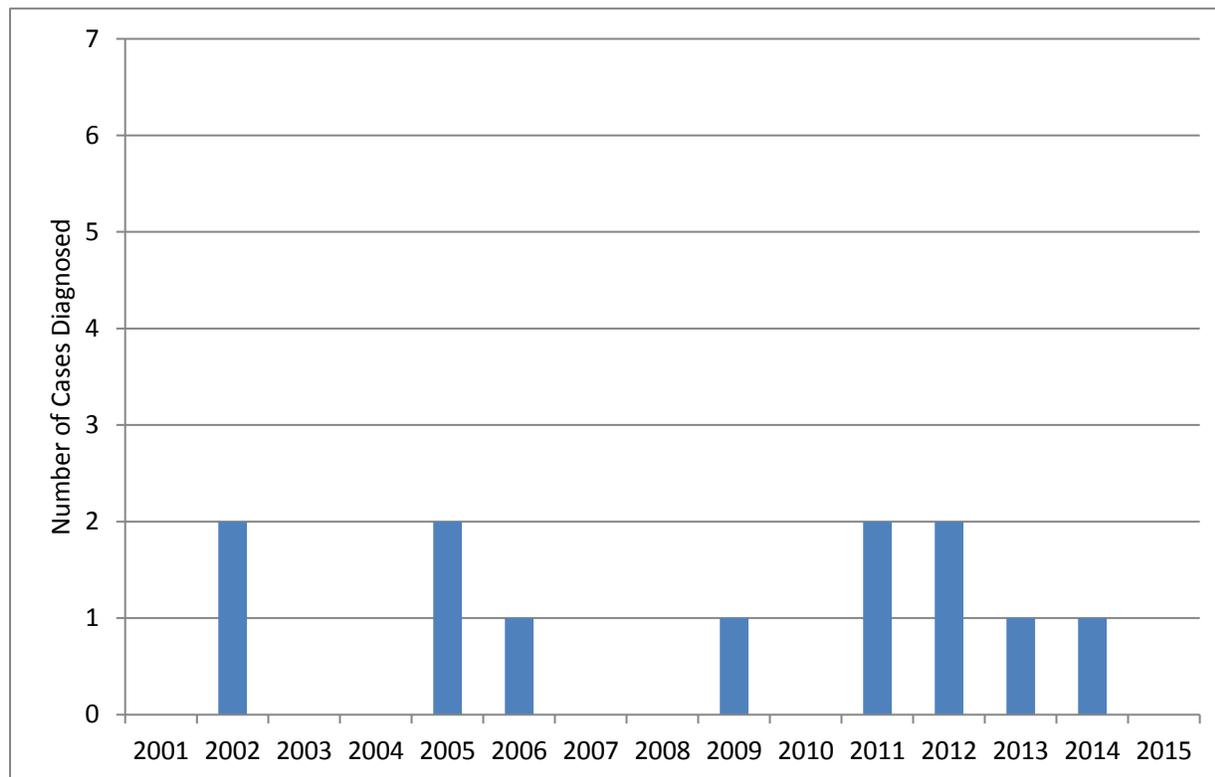
CHILDHOOD CANCER

Cancer Types

Cancer is a collection of related diseases involving cells that begin to divide and spread abnormally. Cancer can affect any organ or cell type in the body resulting in many different diseases. Each cancer type is a distinct disease with a unique set of causes, risk factors, and other characteristics.

Cancers are classified into groups to be studied and treated more easily. Cancers are grouped by their cell type (histology) and where in the body they originate (primary site). There are important differences between adult and childhood cancers. Separate classification schemes have been developed to accommodate these differences. The cancers most frequently diagnosed in adults start in one type of cell, epithelial cells, and are classified into a group known as carcinomas. Because many adult cancers affect this one cell type, they are grouped based on where they start in the body (e.g., the breast, lung, or prostate). However, carcinomas are uncommon in children. The most frequently diagnosed cancers in children (leukemias, brain and central nervous system tumors, and lymphomas) start in a variety of cell types. Therefore, cell type (i.e.,

histology) plays a larger role in classifying childhood cancers (Birch and Marsden 1987; Steliarova-Foucher et al. 2005). The International Classification of Childhood Cancers (ICCC) was developed to accommodate the specific types of cancer diagnosed in children (Steliarova-Foucher et al. 2005). This study classifies childhood cancer using the third edition of the ICCC, updated for Hematopoietic codes based on WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Swerdlow et al. 2008). The types of cancer affecting Wilmington children during the full study period, 1990-2000, varied as shown in Table 2 (note that no children were diagnosed during 1987 to 1989 as shown in

Figure 2).

Table 2. Types of Cancer Diagnosed Among Wilmington Children, 1990-2000

Leukemias
Lymphomas
Malignant Bone Tumors
Central Nervous System Neoplasms
Soft Tissue Sarcomas
Germ Cell Tumors
Renal Tumors
Hepatic Tumors
Other Malignant Epithelial Neoplasms and Malignant Melanoma

Causes of Childhood Cancer

A series of changes to a cell's genetic material results in the conversion of a normal cell to a tumor cell (Barrett 1993; Knudson 1971; Loeb et al. 2003). Many cancers occur because of changes to cells that happen by random chance. These are called sporadic or spontaneous mutations and are not due to any particular exposure to a cancer-causing agent (i.e., carcinogen). Other times, exposure to a carcinogen may be an initiating or contributing factor to the development of cancer in an individual. It is possible that multiple risk factors may influence the development of cancer and an individual's risk of developing cancer may depend on a complex interaction between their genetic makeup and exposure to a cancer-causing agent (Wu et al. 2018).

For childhood cancers, the initial genetic change (e.g., gene mutation) can occur during childhood or in the fetus during pregnancy. In some cases, certain mutations that increase the risk of developing cancer can be passed down from parent to child. About 10% of children diagnosed with cancer have one of several rare genetic syndromes that

increase their risk of developing cancer (Roman et al. 2018). However, not all children with a predisposition syndrome will develop cancer. An additional mutation (or mutations) needs to occur to change normal cells to cancer cells (Barrett 1993; Knudson 1971).

Both genetic factors and various prenatal and postnatal exposures have been extensively evaluated as potential risk factors for childhood cancer, although most causes of childhood cancer remain unknown (NCI 2019). Lifestyle-related risk factors such as body weight, physical activity, diet, and tobacco use play a major role in many adult cancers. However, since these factors usually take many years to influence cancer risk they are not thought to play much of a role in childhood cancers (ACS 2019). Some risk factors for childhood cancer have been identified, but account for only a small portion of all diagnoses. Widely accepted risk factors include ionizing radiation, certain genetic diseases, some viral infections, and certain medications (Roman et al. 2018).

Risk Factors and Epidemiology of Cancer Types Diagnosed Among Wilmington Children

A total of 23 cancers were diagnosed among Wilmington children between 1990 and 2000.

Following is a review of the literature describing the epidemiology and potential causal factors of childhood cancer presented by cancer type.

<u>Leukemia</u>
Eight children in Wilmington were diagnosed with leukemia between 1990 and 2000. Six of the children were diagnosed with acute lymphocytic leukemia (ALL) and the other two were diagnosed with acute myeloid leukemia (AML). A ninth child also had a diagnosis of leukemia but that cancer occurred several years after an earlier diagnosis of malignant bone tumors and was likely related to treatment received from the earlier cancer (Bradley et al. 2018). This child's initial cancer diagnosis (malignant bone tumors) was included in the study, but the later diagnosis of leukemia was excluded.

Leukemia is a cancer of the bone marrow and blood (ACS 2014). It is the most common type of childhood cancer and accounted for slightly more than 27% of all cancers diagnosed in children in the US and 24% in Massachusetts during 2000-2009 (MCR 2014).

In children, leukemia is classified into five subgroups: lymphoid leukemias, including ALL; AML; chronic myeloproliferative diseases; myelodysplastic syndrome and other

myeloproliferative diseases; and unspecified and other leukemias (Steliarova-Foucher et al. 2005). ALL is the most common type of leukemia in children. During 2000-2009, ALL accounted for about 76% of leukemia diagnoses nationally and 78% of leukemia diagnoses in Massachusetts (MCR 2014). Peak occurrence of ALL is between two and four years of age. AML accounts for most of the remaining leukemia diagnoses among children. Diagnoses of AML are more spread out across the childhood years, but it is slightly more common during the first two years of life and during the teenage years (ACS 2014). While ALL is more common among boys than girls, AML occurs equally among boys and girls (MCR 2014; Noone et al. 2018).

While some genetic conditions, such as Down's syndrome, increase the risk of childhood leukemia, most cases of leukemia are not linked to any known genetic cause. Brothers and sisters of children with leukemia have a slightly increased chance of developing leukemia, but the overall risk is low. Siblings with an identical twin with leukemia, however, have a higher risk (Ross and Spector 2006).

Exposure to high levels of ionizing radiation is a known risk factor for childhood leukemia. Japanese atomic bomb survivors had a greatly increased risk of developing leukemia, particularly AML (de Gonzalez et al. 2018). Studies of pregnant women receiving abdominal X-rays during the 1950s and 1960s show an increased risk of acute leukemia in their children. Some studies have also shown an increased risk from medical X-rays during childhood (Roman et al. 2018). Today, medial x-rays use lower doses and guidelines for doctors have been developed to protect pregnant women and children (US FDA 2019; NCI 2019). Research assessing current risks from fetal or childhood exposure to medical radiation from x-ray tests and CT scans is ongoing. Some studies have found a slight increase in risk, while others have found no increased risk (US FDA 2019; NCI 2019; Roman et al. 2018).

Certain chemicals and chemotherapy drugs may increase the risk of leukemia (ACS 2014). Previous chemotherapy treatment with alkylating and platinum agents is associated with an increased risk of developing AML (Bradley et al. 2018; Roman et al. 2018). Some studies show a link between parental exposure to solvents, paints, and vehicle exhaust (Colt and Blair 1998; Miligi et al. 2013). Many studies focus on exposures to benzene, which is a known carcinogen and commonly found in gasoline, vehicle exhaust, paints, glues, and industrial emissions. The International Agency for Research on Cancer (IARC) concludes that exposure to benzene increases the risk of AML in adults and may increase the risk of AML and other types of leukemia in children (ATSDR 2007; IARC 2018). Generally, studies show a stronger link between chemical exposure and AML than with ALL (ACS 2014; Freedman et al. 2001).

Some studies have found a link between chemical contamination in drinking water and childhood cancer. In 1997, the MDPH reported an association between mothers exposed during pregnancy to drinking water contaminated with chlorinated solvents and subsequent diagnosis of leukemia in children in Woburn, Massachusetts (Costas et al. 2002). Two later community-based studies also found links with prenatal exposure to chlorinated solvents and other contaminants in drinking water and leukemia. In 2003, the New Jersey Department of Health and Senior Services reported an association in girls, but not boys in Dover Township, New Jersey (Fagliano et al. 2003). In 2013, ATSDR reported a weak association in children born to mothers living at the Marine Corps Base Camp Lejeune in North Carolina (Cantor et al. 2018; Ruckhart et al. 2013).

The link between leukemia and pesticides has been studied extensively. Studies have found a link between childhood leukemia and household exposure to pesticides, either during pregnancy or during early childhood. Studies of parental workplace exposure to pesticides have also identified an association with childhood leukemia (Chen et al. 2015; Infante-Rivard and Weichenthal 2007; Van Maele-Fabry et al. 2011; Whitehead et al. 2016; Zahm and Ward 1998). While some studies did not find links between residential and parental occupational pesticide exposure and childhood leukemia, summary evidence from recent meta-analyses support these associations (Van Maele-Fabry et al. 2010, 2019; Wigle et al. 2009).

According to the US Surgeon General, smoking increases the risk of AML (US HHS 2014). The most recent IARC evaluation of cancers related to tobacco smoking concluded that parental smoking increases the risk of childhood leukemia, particularly ALL; the positive associations were most consistent between paternal and combined parental smoking, while maternal smoking was less consistently associated with childhood leukemia (IARC 2012). Similarly, a meta-analysis by Liu et al. (2011) shows a positive association between childhood ALL and paternal ever smoking at various time periods of exposure between pre-conception and after birth.

High birth weight, commonly defined as greater than 4,000 grams, is associated with increased risk for leukemia in a number of epidemiological studies (Roman et al. 2013). The reason for this association is unknown, but similar observations have been made for other cancer types (Roman et al. 2018).

Other factors have been studied for a possible link to childhood leukemia but results have not been consistent or have not demonstrated strong links. Some studies have suggested that maternal alcohol consumption during pregnancy might increase the risk of leukemia in children (Latino-Martel et al. 2010). Other exposures investigated include electromagnetic fields (such as living near power lines), living near a nuclear

power plant, infections early in life, mother's age when child is born, and fetal exposure to hormones such as diethylstilbestrol (DES) or birth control pills, but research has not produced conclusive results (Eden 2010; Roman et al. 2018).

<u>Lymphomas</u>
Lymphoma was diagnosed in three Wilmington children between 1990 and 2000. Two children were diagnosed with Hodgkin lymphoma and one child was diagnosed with non-Hodgkin lymphoma (NHL).

Lymphomas are cancers that start in the cells of the lymph system, which is part of the body's immune system. Lymphoma (including both NHL and Hodgkin lymphoma) is the third most common cancer in children and accounted for about 17% of childhood cancers in Massachusetts and 14% in the US during 2000-2009 (MCR 2014). In the US and Massachusetts, half of childhood lymphomas are Hodgkin lymphoma, about a third are NHL (excluding Burkitt lymphoma), and about 10% are Burkitt lymphoma. Lymphoma incidence increases with age (MCR 2014).

NHL can occur at any age but is rare in the first year of life. During 2000-2009, 78% of NHL diagnoses among children in Massachusetts occurred after the age of 14. NHL is more than two times more common in boys than in girls. In Massachusetts, two-thirds of non-Hodgkin lymphoma diagnoses are among boys. The reasons for this sex difference are not known (Bleyer et al. 2006; MCR 2014; Noone et al. 2018; Ries et al. 1999).

Children with a family history of lymphoma have a greater risk. Children with a sibling or parent with NHL have a greater risk of being diagnosed with NHL. This pattern is likely related to shared genetic and environmental factors (Cerhan et al. 2018; Roman et al. 2018). Children with certain genetic syndromes, such as Li-Fraumeni syndrome, have a higher risk of developing non-Hodgkin lymphoma (Roman et al. 2018).

Epstein-Barr virus infection (which is associated with infectious mononucleosis) has been implicated in non-Hodgkin lymphoma. Children with a weakened immune system, such as those taking immunosuppressant drugs following an organ transplant, and children with human immunodeficiency virus are at increased risk of lymphoma (Cerhan et al. 2018; Roman et al. 2018).

Studies indicate that certain chemicals are associated with non-Hodgkin lymphoma. Studies in adults suggest that non-Hodgkin lymphoma risk may increase with exposure to solvents in the workplace (Wang et al. 2009). Parental exposures to solvents, vehicle exhaust, and heavy metals have been associated with increased childhood risk of non-

Hodgkin lymphoma (Miligi et al. 2013). Benzene and polychlorinated biphenyls (PCBs) are categorized by IARC as carcinogens. IARC evaluations of these chemicals conclude that they may increase the risk of non-Hodgkin lymphoma (IARC 2016; 2018).

As seen with brain cancer and leukemia, studies demonstrate an association between pesticide exposure and non-Hodgkin lymphoma in children either through parental occupational exposures or in-home exposures (Chen et al. 2015; Infante-Rivard and Weichenthal 2007; Zahm and Ward 1998).

Ward et al. (1996) found that drinking water contaminated with nitrate increases the risk of non-Hodgkin lymphoma. However, subsequent studies of nitrate and nitrite exposure from drinking water and diet show mixed results (Aschebrook-Kilfoy et al. 2013; Chiu et al. 2008; Ward et al. 2006).

Some studies show an association with high birth weight and increased risk for non-Hodgkin lymphoma. However, not all studies confirm this association (Roman et al. 2018).

Hodgkin lymphoma occurs most often in children older than 10 and is rare in children under five. It is the most common cancer in adolescents, accounting for about 15% of cancer diagnoses in teenagers aged 15 to 19 (ACS 2014; MCR 2014; Noone et al. 2018). Hodgkin lymphoma is slightly more common among males. In Massachusetts, boys make up slightly more than half of Hodgkin lymphoma diagnoses (Bleyer et al. 2006; MCR 2014; Noone et al. 2018;Ries et al. 1999). Siblings, especially identical twins, of children with Hodgkin lymphoma are more likely to develop Hodgkin lymphoma (Roman et al. 2018).

Based on the epidemiological and medical literature, no environmental risk factors have been identified, with the exception of exposure to the Epstein-Barr virus. People who have had infectious mononucleosis (sometimes called *mono* for short), an infection caused by the Epstein-Barr virus, have an increased risk of Hodgkin lymphoma. As stated earlier, Epstein-Barr virus infection has also been implicated in non-Hodgkin lymphoma but the connection is less clear. Some studies show increased risk of Hodgkin lymphoma in people with a higher socioeconomic background. One possible explanation is that children from more affluent families might be exposed to some type of infection (such as Epstein-Barr virus) later in life than children from less affluent families, which might somehow increase their risk. Children with a weakened immune system and children with human immunodeficiency virus are at increased risk of Hodgkin lymphoma (Hjalgrim et al. 2018; Roman et al. 2018).

Malignant Bone Tumors
Three Wilmington children were diagnosed with bone cancer between 1990 and 2000. All three were diagnosed with Ewings Family of Tumors (EFOT), which is a group of cancers that start in the bones or nearby soft tissues that share some common features. EFOT consists of Ewing sarcoma, extraosseous Ewing tumor (also known as extraskeletal Ewing sarcoma), and peripheral primitive neuroectodermal tumors (pPNET). Specifically, one child in Wilmington was diagnosed with Ewing sarcoma and the other two were diagnosed with pPNETs.

Malignant bone tumors accounted for about 5% of all childhood cancers in the US and about 4% in Massachusetts during 2000-2009. EFOT accounted for 31% of bone cancers among children in the US and 36% in Massachusetts during 2000-2009 (MCR 2014), making EFOT diagnoses account for only about 1% of all childhood cancers. Most diagnoses of EFOT occur in the early teenage years for unknown reasons, but they can also occur in younger children as well as in adults (Ries et al. 1999). The most common type of bone cancer in children, osteosarcoma, accounts for about 60% of all childhood bone cancers in Massachusetts (MCR 2014), but was not present among the cancers in Wilmington from 1990-2000.

Ewing sarcoma occurs more frequently among populations of European descent. Genetic research to identify the source of this predisposition is ongoing (Grunewald et al. 2018; Roman et al. 2018). Nearly all EFOT cells include a mutation in a specific gene. This gene mutation is not inherited, but occurs after conception. It is not clear what might cause the genetic change (US NLM 2019).

Central Nervous System (CNS) Neoplasms
The category of CNS neoplasms includes miscellaneous intracranial and intraspinal neoplasms. One Wilmington child was diagnosed with a CNS tumor called astrocytoma.

CNS tumors include tumors that arise from the brain, spinal cord, and other sites within the skull and spinal cord (Roman et al. 2018). Nationally and statewide, CNS tumors are the second most common type of cancer in children. CNS tumors accounted for about 17% of all childhood cancers in the United States and about 19% of all childhood cancers in Massachusetts during 2000-2009 (MCR 2014; ACS 2014). Astrocytomas are the most common type of CNS cancer and accounted for about half of all CNS cancers among children in the US and Massachusetts during 2000-2009 (Bleyer et al. 2006; MCR 2014).

Children with certain genetic syndromes, such as neurofibromatosis, Li-Fraumeni syndrome, and tuberous sclerosis, have a higher risk for brain and CNS tumors (Roman et al. 2018).

The most well-established environmental risk factor for brain and CNS tumors is ionizing radiation exposure to the head, most often from the treatment of other cancers (Pollack and Jakacki 2011). Historically, before the risks of radiation were well known (more than 50 years ago), children with ringworm of the scalp (a fungal infection) often received low-dose radiation therapy and were found to have an increased risk of brain tumors as they got older (Ron et al. 1988). More recently, children received radiation exposure to the head as treatment for leukemia. These brain tumors usually develop around 10 to 15 years after the radiation treatment (Neglia et al. 1991).

The possible risk from exposure to medical imaging tests that use radiation, such as x-rays or CT scans, is not fully understood and research is ongoing. A recent study shows a small increased risk, but more research is necessary to confirm this finding (Roman et al. 2018). Guidelines recommending appropriate radiation levels for tests on children and asking doctors to order these tests only when absolutely necessary have been developed to help doctors protect children (US FDA 2019).

Studies investigating the risk of CNS tumors in children and exposure to non-ionizing radiation from electromagnetic fields (EMF) from sources such as residential appliances and power lines have found little evidence of an association (Feychting and Schuz 2018). Risk of exposure to radio-frequency EMF, such as from mobile phones and other wireless devices, is an active area of research; most studies evaluating a link to CNS cancer have failed to find an association, however, and very little of the research has been in children. Overall, epidemiological evidence does not suggest non-ionizing radiation from EMF as a risk factor for CNS tumors in children (Feychting and Schuz 2018; Roman et al. 2018).

Prenatal and postnatal pesticide exposure in the home environment as well as through parental occupations is thought to be associated with brain cancers (Bagazgoitia et al. 2018; Feychting et al. 2001; Infante-Rivard and Weichenthal 2007; Pogoda and Preston-Martin 1997; Shim et al. 2009; Zahm and Ward 1998). Brain cancers in children have also been found to be associated with parental exposure to chemicals such as chlorinated solvents and heavy metals (Colt and Blair 1998; Johnson et al. 2014).

Studies evaluating risk factors for CNS cancer have included the ingestion of nitrates and nitrites. Ingestion of food is the main source of exposure to nitrates and nitrites, but contaminated drinking water can contribute to overall exposure. In the stomach, nitrite

reacts with some types of amines and amides to form NDMA and other *n*-nitroso compounds. Ingested nitrate is converted to nitrite in saliva, which increases nitrite available for conversion into NDMA and other *n*-nitroso compounds (IARC 2010). An increased risk of childhood brain cancer has been reported following maternal nitrite intake from cured meats during pregnancy (Preston-Martin et al. 1996; Pogoda and Preston-Martin 2001; Pogoda et al. 2009; Nielsen et al. 2011). Maternal ingestion of nitrite from drinking water during pregnancy is also associated with an increased risk of brain tumors in children, but the results were limited to astroglial tumors and other studies have not shown a link (Mueller et al. 2004). There is little evidence of an association between brain cancer and ingestion of nitrate (IARC 2010).

High birth weight has been associated with brain and CNS cancers in a number of epidemiological studies (Johnson et al. 2014).

Soft Tissue Sarcomas
One Wilmington child was diagnosed with rhabdomyosarcoma between 1990 and 2000.

Soft tissue sarcomas are cancers that develop in connective tissues, such as muscle, fat and blood vessels, and can occur at any site throughout the body. Soft tissue sarcomas accounted for about 7% of all childhood cancers in Massachusetts during 2000-2009, which coincided with national trends (MCR 2014; Ries et al. 1999). There are many different types of soft tissue sarcomas. The most common type of childhood soft tissue sarcoma is rhabdomyosarcoma, which develops in skeletal muscle. Rhabdomyosarcomas make up about 2.4% of childhood cancers in Massachusetts and 2.9% in the US (MCR 2014). Although the incidence of soft tissue sarcomas is highest among young children during infancy and children aged 15 to 19 years old, more than half are diagnosed by age 10 (Ries et al. 1999). The incidence in Massachusetts follows this pattern (MCR 2014).

There are few established risk factors for rhabdomyosarcoma. Some rare genetic syndromes (e.g., Li-Fraumeni) increase risk but only account for a small number of diagnoses. Some studies have suggested that exposure to X-rays during pregnancy might be linked with an increased risk of rhabdomyosarcoma in young children (Roman et al. 2018). Parental use of drugs such as marijuana and cocaine has also been suggested as a possible risk factor but these have been small studies, and more research is needed (Grufferman et al. 1993).

Germ Cell Tumors
Two children in Wilmington were diagnosed with germ cell tumors between 1990 and 2000. Both were of the type known as intracranial and intraspinal germ cell tumors.

Germ cell (egg or sperm), trophoblastic (cells outside an early embryo), and other gonadal (ovarian or testicular) tumors arise from reproductive cells. These cancers accounted for about 6% of all childhood cancers in Massachusetts and about 7% in the US during 2000-2009. The majority of these cancers (about 65%) are gonadal germ cell tumors, located in either the ovaries or testes (MCR 2014). Intracranial and intraspinal germ cell tumors are those that develop when the sex cells, normally found in the ovaries and testes, do not migrate to their proper location during fetal development and become trapped in the brain. They are most frequently found around the pituitary and pineal glands (Roman et al. 2018). Intracranial and intraspinal germ cell tumors accounted for about 13% of all germ cell tumors in Massachusetts and about 16% in the US during 2000-2009 (MCR 2014), accounting for <1% of all childhood cancers. While the incidence of germ cell tumors as a whole increases sharply in males after age 14 and more gradually among females, the incidence of intracranial and intraspinal germ cell tumors is relatively constant among children of all ages. There are no established risk factors for intracranial and intraspinal germ cell tumors (Roman et al. 2018).

Renal Tumors
One Wilmington child was diagnosed with nephroblastoma (also called Wilms' tumor) between 1990 and 2000.

Renal tumors are cancers that originate in the kidney. In the US and Massachusetts, about 4% of all cancers in children were renal tumors during 2000-2009. Wilms' tumor is the most common type of kidney cancer in children, accounting for 89% of kidney tumors in Massachusetts (MCR 2014; Ries et al. 1999). These cancers tend to occur in young children. Nationally, the average age at diagnosis is about 3 to 4 years. The disease becomes less common as children grow older and is uncommon after age 6. Wilms' tumor is slightly more common in girls than boys (ACS 2014).

Wilms' tumor is more common in children with certain genetic syndromes, such as Beckwith-Wiedemann syndrome and others. About 10% of children with Wilms' tumor also have certain birth defects, including aniridia, hemihyperplasia , cryptorchidism, and hypospadias. Only about 2% of children with Wilms' tumors have a family history of the cancer. Scientists think that these children inherit an abnormal gene that increases their risk of developing Wilms' tumor (NCI 2019).

Studies show that high birth weight is consistently associated with increased risk for Wilms' tumor (Roman et al. 2018). No environmental risk factors have been identified for Wilms' tumor (Roman et al. 2018).

Hepatic tumors
One child in Wilmington was diagnosed with hepatoblastoma between 1990 and 2000.

Hepatic tumors are cancers that originate in the liver. Hepatic tumors are rare in children and accounted for about 1.1% of childhood cancers in Massachusetts and 1.3% in the US during 2000-2009 (MCR 2014). Hepatoblastoma is the most common type, accounting for about 85% of childhood hepatic tumors cancers in Massachusetts (MCR 2014). Rates of hepatoblastoma are highest among children 3 years of age and younger (Roman et al. 2018).

Some genetic disorders (e.g., Beckwith-Wiedemann syndrome, familial adenomatous polyposis, and Aicardi syndrome) increase a child's risk of being diagnosed with hepatoblastoma (Roman et al. 2018).

There are few clues to the cause of this cancer in children. IARC concluded that parental tobacco smoking may increase the risk of hepatoblastoma (IARC 2012). Very low birth weight has been linked with hepatoblastoma (Roman et al. 2018). Some research suggests parental occupational exposure to oil products, paints, or metals (e.g., soldering fumes), particularly by the mother during pregnancy, may increase the risk of hepatoblastoma in children, but more research is necessary (Buckley et al. 1989; Janitz et al. 2017).

Other Malignant Epithelial Neoplasms and Malignant Melanoma
In Wilmington, one child was diagnosed with a skin adenocarcinoma - specifically, a sweat gland adenocarcinoma (eccrine papillary adenocarcinoma) between 1990 and 2000. A second child (a teenager) was diagnosed with a cancer of this type, a malignant melanoma. This child was excluded from the study because exposure to sunlight is the major risk factor for most melanomas with 80% of primary melanomas carrying UV signature mutations (Armstrong et al. 2018).

In general, malignant epithelial tumors develop from epithelial cells that can be located in the lining of organs and different parts of the body, including the skin (Roman et al. 2018). As a group, these cancers accounted for about 10% of childhood cancers in the US and 11% in Massachusetts during 2000-2009. About 97% of these cancers in Massachusetts children were diagnosed after age 14. The most common types of these cancers are thyroid carcinoma and malignant melanoma (MCR 2014; Roman et al. 2018).

Skin carcinomas (that are not histologically a melanoma nor a basal or squamous cell carcinoma) make up less than 1% of this group (MCR 2014). More specifically, sweat

gland adenocarcinomas are rare with 687 diagnoses reported among individuals of all ages to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute from 1973 to 2014. The median age at diagnosis is 67 and about 60% of cases occur in females (Dang and Chin 2018). There are no established risk factors for sweat gland adenocarcinomas; however, a review of case reports indicated that previous radiotherapy, exposure to ultra violet radiation (e.g., sun exposure), and a weakened immune system may increase risk (Gordon et al. 2017).

ENVIRONMENTAL CONCERNS

Through meetings with the Wilmington Childhood Cancer Community Advisory Committee and research of public records, such as those produced and compiled by the US EPA, MA DEP, and the Wilmington BOH, sources of environmental concern and potential exposure were identified. Concerns raised by residents included air pollution from nearby industries, indoor air pollution from trichloroethylene (TCE)-contaminated groundwater, and possible bedrock aquifer contamination by volatile organic compounds (VOCs) in the Kelly Hill area. Local air contamination data from nearby industries was evaluated by MA DEP and determined to be a nuisance, but not a toxicity concern. MA DEP also noted that the TCE contamination was not in shallow groundwater and was, therefore, unlikely to cause an indoor air pollution problem. After a review of available data, the two environmental exposures of principal interest remained groundwater and public drinking water concerns from TCE and NDMA contamination.

Olin Chemical Site

The Olin Chemical facility encompasses a 53-acre property located at 51 Eames Street in Wilmington. The inactive facility is completely fenced and is bounded on the north by Eames Street, on the east by Boston and Maine railroad tracks, on the south by the Woburn/Wilmington town line, and on the west by an inactive Boston and Maine railroad spur. Surrounding the property to the north, east and west are heavy and light industrial facilities, and to the south is a former municipal landfill for the City of Woburn. The closest residential areas are approximately one quarter of a mile west of the Olin Chemical facility along Main Street and Cook Avenue (see

Figure 1).

The Olin Chemical property was used for chemical manufacturing starting in 1953 by National Polychemicals, Inc. (NPI). Between 1953 and 1971, NPI was owned and operated by American Biltrite Rubber Co., Fisons Limited, and Fisons Corporation. In

1968, Stepan Chemical Corporation purchased NPI and operated the facility until it was purchased by Olin Corporation in 1980. During the 33-year history (1953-1986) of chemical manufacturing at the Olin Chemical site, many different chemicals were produced including acids and bases, phthalates, oxidizing agents, phenols, metal salts, alkenes, alcohols, and aldehydes (MACTEC 2003b). The facility closed in 1986, but the property is still owned by Olin Corporation. The Olin Chemical site was listed as a federal National Priorities List Superfund site in 2006.

Historical wastewater disposal practices were a major source of subsurface contamination both on and off the Olin Chemical property resulting in contamination of the Maple Meadow Brook (MMB) aquifer and the closure of four municipal drinking water supply wells in 2002. The fifth well, Town Park Well, was closed in 2003. Prior to 1970, all liquid wastes were discharged directly into several unlined pits and ponds in the central portion of the property, as well as into a man-made excavation called Lake Poly Liquid Waste Disposal Area (Lake Poly). In 1970, Stepan Chemical installed an acid treatment and neutralization system and new lined lagoons to replace the unlined pits and ponds. Treated wastes were released into the lagoons where calcium sulfate sludge settled out. The lagoons were periodically dredged and the sludge was deposited in a landfill in the southwest corner of the property (now known as the Calcium Sulfate Landfill). Residual liquid wastes were released to an unlined on-property ditch system until 1972, but the discharge was diverted to the municipal sewer when it was constructed in 1972 (CRA 1993; MACTEC 2003a).

The principal contaminants associated with the site include ammonia, chloride, sodium, sulfate, chromium, and NDMA, a probable human carcinogen. NDMA was not used, produced, or disposed of by the Olin Chemical facility. However, many of the chemicals used and produced on the site were nitrogen containing compounds, including ammonia, amides, nitrosamines, and amines. It has thus been hypothesized that the high levels of NDMA observed in groundwater beneath the site resulted from chemical reactions that occurred after wastes that were produced at the Olin Chemical site were released and entered the groundwater (MACTEC 2003a) (see Appendix C for more detail). The discovery of NDMA in the MMB aquifer resulted in the closure of four of the five municipal drinking water wells drawing water from the MMB aquifer (MACTEC 2005).

Ongoing US EPA site clean-up studies are separately addressing three areas of the site: the former facility property, including all contamination except groundwater contamination; off-facility areas of sediment, surface water and soil; and all groundwater. Substantial cleanup work has been completed on the Olin Chemical property, including the installation of a temporary cap and slurry wall to manage the source of groundwater contamination. The Olin Chemical property is fenced and public access to known contaminated areas is

restricted. More details about the Olin Chemical site can be found on the US EPA's Superfund website for the facility (US EPA 2019).

Maple Meadow Brook Aquifer

The MMB aquifer is an important factor in environmental concerns for two reasons. One is that it served as a source of public drinking water beginning prior to 1974, the initial year of interest for drinking water information in this study. The second is that groundwater flows beneath the Olin Chemical site to the aquifer. The groundwater flow beneath the Olin Chemical site reflects the bedrock and surface topography but is modified by groundwater pumping (Geomega 2001a, 2001b). Although relatively little surface water drains northward from the Olin Chemical site, there is northward groundwater flow from the site. Groundwater from the northern and western parts of the site flows west and north, eventually to the MMB aquifer. Groundwater from the eastern and southern parts of the site flows east and south, where it discharges to shallow ditches near the eastern boundary of the Olin Chemical site and then flows south to the Aberjona River.

The manufacture of a broad range of products at the Olin Chemical facility produced a variety of wastes that were highly salty and acidic (CRA 1993), including a complex mixture of inorganic chemicals and at least 196 organic chemicals. Because salt water is denser than freshwater, it will settle in low areas on the underlying bedrock (Smith 1997). In Wilmington, this resulted in the creation of two pools of Dense Aqueous-Phase Liquid (DAPL) on the bedrock surface west of the Olin Chemical site (AMEC 2013). A DAPL is a liquid that is denser than water. A DAPL can dissolve in water, but groundwater conditions typically provide poor opportunity for mixing and DAPL layers often sink to the bottom and dissolve slowly over time into the overlying aquifer. In contrast, LNAPLs (non-aqueous-phase liquids that are less dense than water) and DNAPLs (non-aqueous-phase liquids that are denser than water) are liquids that are only sparingly soluble in water. As a result, subsurface spills of LNAPLs such as gasoline and home heating oil tend to float on aquifer surfaces, while subsurface spills of DNAPLs such as pure-phase chlorinated solvents tend to sink to the bottom of aquifers. NAPLs are typically hundreds to thousands of times less soluble in water compared to DAPLs.

The DAPL from the Olin Chemical property wastes is characterized by a variety of inorganic (e.g., ammonia, chloride, sodium, and sulfate) and organic compounds (e.g., NDMA, acetone) (Smith 1997). The direction of groundwater flow within the MMB aquifer is generally northward past the DAPL pools, which causes groundwater flowing past the pools to become contaminated by chemicals from the DAPL, including NDMA. MACTEC (2007) reported NDMA concentrations as high as 25,000 nanograms per liter (ng/L) at monitoring wells in the DAPL zone.

Principal Contaminants of the Wilmington Public Drinking Water System

The Wilmington drinking water distribution system is the network of underground water supply mains that transports treated drinking water from the treatment plants to residences, businesses, and other users. The period of interest in the system for this study is 1974-2000. During that time period, the Wilmington municipal water supply sources were nine groundwater wells, five of which were in the MMB aquifer in southern Wilmington (Butters Row 1 and 2, Chestnut St. 1 and 1A/2, and Town Park). The water from these wells began being processed at the Butters Row Water Treatment Plant after it was brought online in June 1981. The Shawsheen Ave. well in the western part of town was connected to the Butters Row Water Treatment Plant in 2000, before which it injected water directly into the water distribution system. The remaining three wells (Brown's Crossing, Salem St., and Barrows) are located in northern Wilmington and produce water that is processed at the Sargent Water Treatment Plant. Figure 4 shows the Wilmington water distribution system along with well and treatment plant locations in the year 2000. The Aldrich Road well shown in the far western part of town has been out of service since 1973.

Figure 4. Map of the Wilmington Water Distribution System in the year 2000
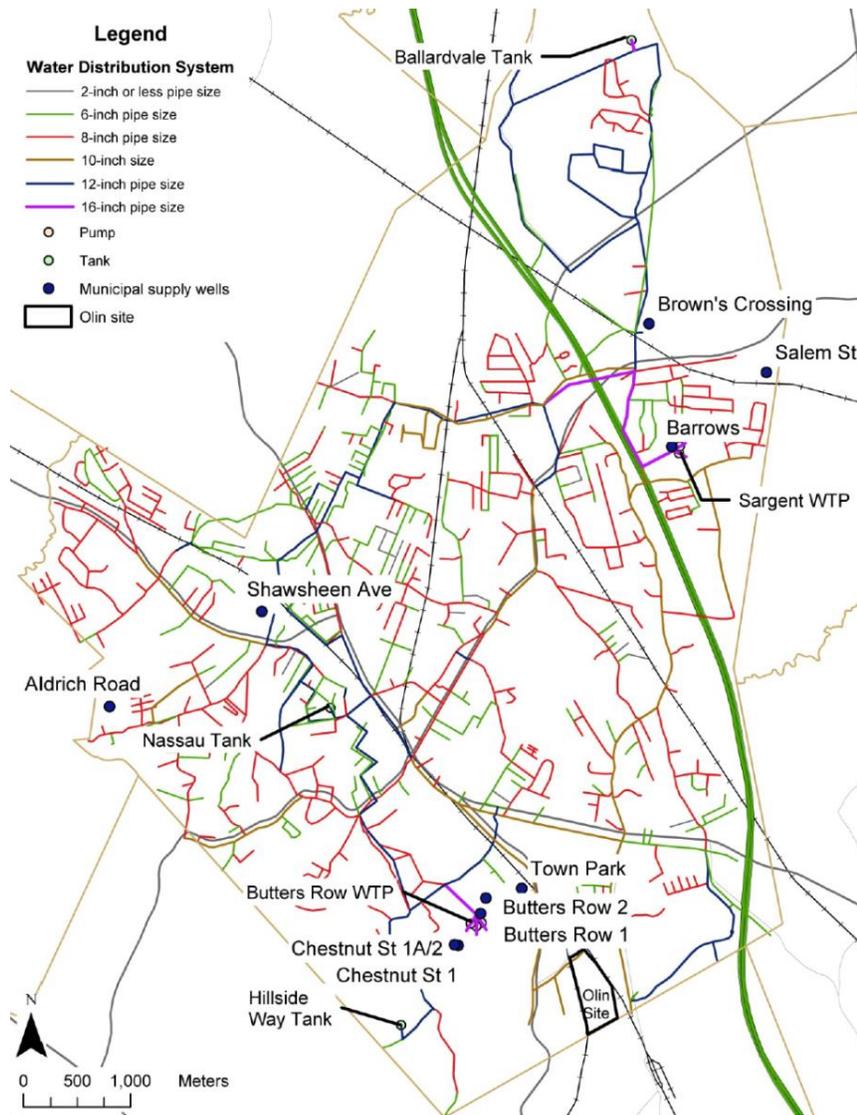
Source: Durant et al., 2018. Modeling *N*-Nitrosodimethylamine And Trichloroethylene Concentrations In The Wilmington, Massachusetts, Water Supply System: 1974 To 2000. Available at: Appendix C, Figure 2.3.

In 2003, testing of the MMB water supply wells revealed NDMA at levels ranging from 32 to 166 ng/L in four of the wells (MACTEC 2003a). No NDMA was detected in water samples from the Town Park well. Samples of finished water collected at the same time at 13 different sites within the drinking water distribution system near the Butters Row Water Treatment Plant showed no detectable NDMA, but the lack of NDMA detection is thought to be because the contaminated wells were not being used at the time of sampling (they were taken offline in 2002). The detections in municipal wells led to

closure of all five MMB wells in 2003 (MACTEC 2005). This decision was based on the MA DEP's drinking water guidance level for NDMA, which is 10 ng/L (MA DEP 2019). There is no drinking water regulatory standard for NDMA.

Routine measurements of water quality in the Wilmington water distribution system were started in the 1970s and continue to the present. Due to changes in regulatory testing requirements over the years, measurements are varied in terms of the compounds evaluated. In the late 1970s, testing included compounds such as sodium and nitrates and some chlorinated volatile organic compounds (VOCs). Today, many additional chlorinated VOCs, non-chlorinated VOCs, semi-volatile organic compounds, and metals are routinely tested for.

The most commonly detected compounds in municipal wells during the period of interest (1974-2000) were TCE, 1,2-dichloroethylene (1,2-DCE), ammonia, nitrates, nitrites, and trihalomethanes. Drinking water standards or guidelines in finished drinking water were not exceeded for 1,2-DCE, ammonia, or nitrates. Nitrite levels were found to exceed the standard of 1 part per million (ppm) in a couple of dead-end streets in 2000 and 2002 with a maximum measured concentration of 1.3 ppm. Trihalomethanes exceeded the standard of 80 parts per billion (ppb) in a few locations in the distribution system in the early 1980s and again in 2003 (200 ppb maximum). TCE exceeded the standard (5 ppb) in several locations in the distribution system up until the late 1980s (27 ppb maximum).

In the 1980s, chlorinated VOCs were regularly detected in the MMB aquifer supply wells, the Butters Rows Water Treatment Plant, and sampling stations in the Wilmington water distribution system. The highest concentrations were in Butters Row #1 and #2 wells, while lower concentrations were present in the Chestnut St. #1 and Town Park wells. The results also show that TCE (and 1,2-DCE) was present in finished water from the Butters Row Water Treatment Plant, indicating that treatment methods used at the time were not completely effective. As a result, TCE and 1,2-DCE were detected at several sampling locations in the water distribution system. The highest concentrations of TCE measured at these sites were in excess of the current drinking water standard of 5 ppb.

The TCE in the distribution system appears to have been the result of contamination of the MMB aquifer. However, the source of contamination is unclear and there were likely multiple contamination sites, possibly from chemicals used to clean home septic systems. The levels of TCE contamination dropped below detection limits by the late 1980s after new treatment methods were initiated by the Wilmington Water and Sewer Division (Appendix C).

N-nitrosodimethylamine (NDMA)

<u>Chemistry</u>
NDMA is a volatile, yellow, oily liquid of low viscosity. NDMA is no longer used industrially or commercially in the US or Canada, though it may still be used in other countries in rubber formulations as a fire retardant and in the organic chemical industry as an intermediate, catalyst, antioxidant, additive for lubricants, and softener of copolymers (ATSDR 1989; Budavari et al. 1989). However, it can be formed from precursors in wastewater and released as a byproduct and contaminant from various industries and municipal wastewater treatment plants, including from the manufacture of pesticides, rubber tires, alkylamines, and dyes.

NDMA may also form under natural conditions in air, water, and soil as a result of chemical, photochemical, and biological processes and has been detected in drinking water. Formation can occur due to chemical reaction between ubiquitous, naturally occurring precursors classified as nitrosatable substrates (e.g. secondary amines) and nitrosating agents (nitrite reaction products) (OME 1998). For example, NDMA may form in the air during nighttime as a result of the atmospheric reaction of dimethylamine (DMA) with nitrogen oxides (Cohen and Bachman 1978). Soil bacteria may also synthesize NDMA from various precursor substances, such as nitrate, nitrite, and amine compounds (ATSDR 1989). NDMA can be formed as an unintended disinfection byproduct of the chlorination of wastewater and drinking water at treatment plants that incorporate a chlorination or chloramination process in the presence of nitrogen-containing organic matter (OME 1994; Richardson 2003; Mitch et al. 2003; Bradley et al. 2005). It can be formed in water treatment plants or from groundwater contaminated by industrial effluents (ATSDR 1989). NDMA precursors are widespread throughout the environment, occurring in plants, fish, algae, urine, and feces (Ayanaba and Alexander 1974).

The chemical properties of NDMA can help explain how it is released into the environment. In the atmosphere, NDMA exists as a vapor, does not attach to airborne particles, and rapidly degrades in sunlight by direct photolysis (NDMA half-life of about 5-30 minutes) (Sax and Lewis 1987). In soil, it also does not attach to particles. Consequently, it is very mobile and can leach into groundwater. In surface water, NDMA is also broken down by sunlight though more slowly because of the presence of other suspended particles (half-life of about 16 minutes). In groundwater, it can readily mix with water, lipids, and organic solvents (ATSDR 1989, 1999; HSDB 2019; OME 1991; Thomas 1982; US EPA 2017).

Health Risks

There is overwhelming evidence that NDMA is mutagenic (i.e., causing an increased rate of change in a gene that can lead to cancer), clastogenic (i.e., causing a break in chromosomes that can lead to mutagenesis and possibly cancer) and carcinogenic (ATSDR 1989; IARC 1978, 1987; US EPA 2017). Increased frequencies of gene mutations, chromosomal damage, and gene repairs have been observed in a wide variety of cell assays. Similarly, clear evidence of genetic effects has been observed in animal studies. Notably, these genotoxic effects have been observed in liver, kidney, and lung tissues, based upon where tumors commonly arose following experimental exposure to NDMA and from exposure by germ cells (Gray et al. 1991).

NDMA has been classified by the International Agency for Research on Cancer (IARC) as "probably carcinogenic to humans" (IARC 1987), which was upgraded from its previous classification of "possibly carcinogenic to humans" (IARC 1978). This classification is consistent with that of Environment Canada and Health Canada (Health Canada 2001), which indicates that NDMA is highly likely to be carcinogenic to humans. The European Union categorizes NDMA as a category 1B carcinogen (i.e., presumed to have carcinogenic potential for humans; largely based on animal evidence). In the US, the EPA classifies NDMA as a "probable human carcinogen (category B2)" under its 1986 carcinogen assessment guidelines (US EPA 2017).

Although epidemiological studies are limited, results have been suggestive of an association between exposure to NDMA and several forms of cancer, most consistently with gastric and lung cancer. Exposure to NDMA in these studies has been from the ingestion of foods containing NDMA. Relevant epidemiological studies include case–control investigations of cancer of the stomach (González et al. 1994; La Vecchia et al. 1995; Pobel et al. 1995; Risch et al. 1985), upper digestive tract (Rogers et al. 1995), lung (De Stefani et al. 1996; Goodman et al. 1992), and childhood brain cancer (Huncharek and Kupelnick 2004), in which the potential risks were found to be associated with ingestion of NDMA. There have been no human epidemiological studies of NDMA in drinking water or associations reported between NDMA exposure and leukemia or lymphoma.

Information on non-cancer effects in humans and experimental animals associated with exposure to NDMA is inadequate to characterize exposure–response (WHO 2002).

Sources of Exposure to NDMA

The principal source of exposure to NDMA for humans in the general population, both past and present, is from the ingestion of food (ATSDR 1999). NDMA has been

demonstrated most frequently in beer, cured meat, fish products, and some cheeses. Although levels of NDMA in these products have decreased in recent years as a result of changes in food processing (Sen and Baddoo 1997), ingestion of food containing NDMA precursors (e.g., nitrites and nitrates) can lead to the formation of NDMA in the body. Ingestion of food containing NDMA or NDMA-precursors appears to be responsible for most human exposure to NDMA (Hrudey 2013).

Historically, other sources of exposure to NDMA include consumer products that contain NDMA such as cosmetics, personal care products, and tobacco (ATSDR 1989; Spiegelhalder and Preussmann, 1984). NDMA has also been found in indoor air contaminated with environmental tobacco smoke in the US (Brunnemann and Hoffmann 1978) and in Austria (Klus et al. 1992; Stehlik et al. 1982).

Drinking water has been the most thoroughly studied source of NDMA exposure and it has been reported to be both a past and present source of exposure. However, drinking water sources have been reported to typically contribute only a small proportion of NDMA when compared to food and consumer products (Hrudey et al. 2013; Fristachi and Rice 2007). Zeilmaker's (2010) review of literature presented that the proportion of NDMA intake coming directly from food may be more than 200 times greater than that from drinking water. Hrudey (2013) states that about one third of the U.S. population who receive water from public water supplies in the US are exposed to any NDMA, but concentrations are generally low. Based on the sample data that Hrudey (2013) compiled from major studies surveying the distribution systems of water treatment plants across the U.S., the mean and maximum concentrations ranged between <1 − 1.8 ng/L and 6.8 − 24 ng/L. By comparison, the estimated monthly mean and maximum concentrations modeled across all pipes in Wilmington from 1981-2000 for this study ranged from 5 − 39 ng/L and 12 − 114 ng/L, respectively. In March 1998, 27% of all pipes had concentrations exceeding 100 ng/L.

Overall, research has demonstrated that drinking water, including that contaminated through water treatment efforts, is typically not a significant source of NDMA. Hrudey (2013) estimated that drinking water accounted for up to 0.04% of NDMA exposure in adults and up to 0.3% in infants in the general population. The World Health Organization (2008) and others (Chowdhury 2014) support the view that NDMA from drinking water likely accounts for less than 10% of all NDMA exposure. We note, however, that the contribution of NDMA from drinking water can be much higher if the exposure is from a specific contamination source with concentrations that are much higher than those commonly measured.

Absorption of NDMA through the skin and through inhalation is considered to contribute insignificant amounts to exposure (Health Canada 2011). NDMA absorption through the stomach and intestines is much greater than through the skin partly because of the high rate of volatilization of NDMA in the air before dermal absorption and because NDMA rapidly degrades in sunlight (ATSDR 1999; CalEPA 2006). It has been observed that NDMA may not volatilize significantly in shower air, regardless of the water temperature (Mitch 2003).

Importantly, studies in animals have found that NDMA can be transmitted through the placenta to offspring who then develop cancer (CalEPA 2006), and a laboratory study of human placentas and NDMA also demonstrated transplacental transmission (Annola et al. 2009). These studies suggest a pathway of exposure exists between a mother exposed to NDMA and her fetus.

Existing Drinking Water Health Guidelines

Although NDMA is listed as a priority pollutant in the Code of Federal Regulations (CFR) (40 CFR 136.36), no federal maximum contaminant level (MCL) has yet been established for drinking water (US EPA 2017). However, because of the health risks associated with NDMA exposure and in response to discoveries of NDMA in drinking water supplies, some health guidelines have been adopted by different authorities (

Table 3).

Table 3. Summary of NDMA Drinking Water Guidelines

Authority	Guideline	As ng/L	Explanation
California Environmental Protection Agency[1]	0.003 µg/L	3	Public Health Goal, the level at which adverse health effects are not expected to occur from a lifetime of exposure
California Department of Public Health[2]	0.01 µg/L	10	Notification Level at which drinking water systems are to notify local authorities
California Environmental Protection Agency[2]	0.3 µg/L	300	Response Level that corresponds to the lifetime theoretical excess cancer risk in an adult of 1 in 10,000 and is considered the concentration at which a water supply should be taken out of service
Health Canada[3]	0.04 µg/L	40	Based on cancer end-points in adults and is considered protective of all health effects and is the maximally acceptable concentration in drinking water
World Health Organization[4]	0.1 µg/L	100	Corresponds to lifetime carcinogenicity risk in adults of 1 in 100,000
Massachusetts Department of Environmental Protection[5]	0.01 µg/L	10	Guideline to help evaluate NDMA in drinking water

[1]CalEPA 2006
[2]California SWRCB 2019
[3]Health Canada 2011
[4]WHO 2008
[5]MA DEP 2019

Similar guidelines have been established in Arizona (Sedlak and Kavanaugh 2006), Australia (NHMRC, NRMMC 2018), and the UK (UK DWI 2000). The differences between the various guidelines can be due to different approaches in deriving the guideline value (e.g., different scaling factors) and/or the impact of taking into consideration the concentrations that analytical laboratories were capable of detecting.

Trichloroethylene (TCE)

<u>Chemistry</u>
TCE is a nonflammable and colorless liquid that evaporates quickly into the air. Its most important use worldwide has been as a degreasing agent in the automotive and metals industries. In the US, use as a degreasing agent has declined due to increased

environmental regulations, while its use in the manufacturing of refrigerants has increased. TCE is also widely used as a solvent for extraction and waterless drying and finishing. In addition, TCE is found in adhesives, paint removers, varnishes, lubricants, and spot removers. The compound's use as an inhaled anesthetic, fumigant, and extraction aid for decaffeinating coffee was discontinued in the US (ATSDR 2019).

While widely detected in ambient air, the short half-life of TCE (7 days) indicates that it is not a persistent atmospheric compound. TCE can also be found in surface water through industrial discharges of wastewater streams or wet deposition (i.e., rainwater) and in groundwater through landfill leachate. In contaminated groundwater, TCE may off-gas and migrate into indoor air spaces overlying the contaminated area through a process called vapor intrusion. TCE can also be released into the soil, where it is highly mobile and can percolate to subsurface regions including groundwater. In the subsurface regions, TCE degrades slowly and remains persistent, increasing the potential for vapor intrusion (ATSDR 2019).

Sources of Exposure to TCE
The primary route of exposure to TCE for the general population is through inhalation of ambient air and ingestion of drinking water. TCE that is inhaled or ingested can subsequently enter the bloodstream through the lungs or stomach, respectively. To a lesser extent, TCE exposure can also occur by consumption of contaminated foods or contact with consumer products containing TCE. These consumer products include wood stains, varnishes, and finishes; lubricants; adhesives; typewriter correction fluids; paint removers; and cleaners (ATSDR 2019).

Atmospheric levels of TCE are generally higher in urban or concentrated industrial areas and lower in rural regions. However, indoor air presents a more significant source of exposure to TCE than outdoor air. This is because TCE from groundwater sources can evaporate and migrate into air spaces beneath buildings, eventually entering the indoor air by vapor intrusion. Vapor intrusion, along with off-gassing of TCE-containing building construction and consumer products, can contribute to elevated TCE levels in indoor air. Furthermore, volatilization of TCE during baths or showers can also increase indoor air levels among households that use contaminated water supplies (ATSDR 2019).

Dermal contact is not an important exposure pathway for most people based on available data, but it can occur from contact with soil or water containing TCE. Very small amounts can also move from the air through the skin and into the bloodstream (ATSDR 2019).

Children can be similarly exposed to TCE through inhalation of ambient air and ingestion of drinking water. Intake from these two sources is expected to be greater among children than adults because of their increased ventilation rate and water consumption per kilogram of body weight. Their potential exposure through ingestion of dust or soil is likely to be limited because of TCE's low soil adsorption and volatility, but still higher than adults. For infants, breast milk is a potential source of exposure. A developing fetus may also be exposed to TCE because the compound can cross the placenta (ATSDR 2019).

Health Risks
Available human and animal data indicate that TCE potentially targets the kidney, liver, developing fetus, as well as several body systems. Acute inhalation exposure to TCE can cause irritation of the upper respiratory tract, as well as central nervous system depression, dizziness, confusion, nausea, and even death. Chronic exposure can lead to both cancerous and non-cancerous health outcomes. Studies suggest that the immune system and developing fetus may be particularly sensitive to TCE toxicity. Limited epidemiological data that evaluated exposures to TCE in the workplace or residence and from drinking water reported possible associations between TCE and certain heart defects in the developing fetus. Other studies have also shown that exposure to TCE over the long term can lead to an increased risk of developing some autoimmune conditions, including immunosuppression (ATSDR 2019).

Following its Guidelines for Carcinogen Risk Assessment (US EPA 2005), the US EPA characterized TCE as carcinogenic in humans by all routes of exposure (US EPA 2011). The National Toxicology Program (NTP) lists TCE as reasonably anticipated to be a human carcinogen (NTP 2011) and IARC classifies TCE as "carcinogenic to humans" (Guha et al. 2012; IARC 2014). Epidemiological data provide convincing evidence for a causal association between TCE exposure and kidney cancer in humans based on occupational cohort and case-control studies. There is also some evidence for increased risks for non-Hodgkin lymphoma and liver cancer. However, the human data for these two cancer types are less convincing because reliable information is limited to a few occupational cohort studies. Short-term (e.g., several months or several years) exposure to low levels poses lower risks of developing cancer than a lifetime of daily exposure (ATSDR 2019).

A population that ingested well water contaminated with TCE in Woburn, Massachusetts was reported to have an increase in childhood leukemia (Costas et al. 2002). This was supported by a second study of New Jersey communities, where a significant elevation of total leukemia, childhood leukemia, ALL, and non-Hodgkin lymphoma in females was found after exposures to >5.0 ppb of TCE (Fagliano et al.

2003). However, the associations drawn from these studies between the incidence of leukemia and other cancers and oral exposure to TCE are suggestive and not definitive because exposure was known to be of a mixture of contaminants (ATSDR 2019).

Existing Drinking Water Guidelines
The Massachusetts Office of Research and Standards (ORS) has adopted the maximum contaminant level published by the EPA, of 5 ppb for TCE in public drinking water (MA DEP 2019). This standard was adopted by EPA on January 9, 1989 and has thereafter been applicable in Massachusetts (40 CFR, Section 141.60, Effective Dates, July 1, 2002, edition).

METHODS

COMMUNITY ENGAGEMENT

From the beginning of the Massachusetts Department of Public Health's (MDPH's) investigation into childhood cancer rates in Wilmington, residents, community groups, and the Wilmington Board of Health (BOH) have provided input and impetus to the development and completion of this study. A community group called the Kelly Hill Group was initially responsible for helping to raise awareness about childhood cancer in the Kelly Hill neighborhood of Wilmington, bringing the issue to MDPH's attention with the help of State Representative James Miceli. Later expanding their concerns to other parts of Wilmington, the group was re-named the Wilmington Childhood Cancer Study Subgroup and served as the study's first official community advisory committee, working with MDPH to plan for the case-control study. The advisory committee provided feedback on the study's scope, data collection process, and focus. MDPH and the advisory committee met regularly with the goal of ensuring that the study would address the questions and interests of the community and that expectations were achievable. Project staff also occasionally met to discuss the study's progress with a community group made up of affected families that continues to be active as of the writing of this report.

During the course of the study, the advisory committee expanded to include representatives of the Wilmington BOH, the US EPA, the MA DEP, and state legislators representing Wilmington residents. This final iteration of the advisory committee was named the Wilmington Childhood Cancer Study Advisory Committee and remains active through the study's completion. After the exposure assessment of n-nitrosodimethylamine (NDMA) was complete and the study entered its data analysis phase, MPDH provided regular written progress updates to the advisory committee. MDPH acknowledges the tremendous patience of all concerned residents in awaiting this report and appreciates the commitment of the members of the community advisory committee to this project.

STUDY DESIGN

The Wilmington Childhood Cancer Study is a population-based matched case-control study. This research design is best suited when a small number of cases have been identified and a representative control population is needed. Matching allows for the pairing of cases and controls with respect to similarities other than the disease outcome. When cases and controls are matched on criteria such as age or sex, then these factors are no longer able to influence the results such that any observed associations can be

more easily attributed to the risk factor or exposures under investigation. Such a design also enables a more streamlined approach in which these potentially confounding variables do not need to be accounted for during data analysis and, thus, more statistical power is reserved for evaluating the primary association(s) under investigation—a critical concern when a study's sample size is small.

CASE DEFINITION AND RECRUITMENT

A case was defined as a child who 1) was diagnosed with a first primary cancer prior to their 20th birthday, 2) was diagnosed between January 1, 1990 and December 31, 2000, and 3) was a resident of Wilmington at the time of diagnosis. As described in the Background section, one child with a diagnosis of melanoma was excluded because exposure to sunlight is the major risk factor for that cancer type. Another child, while included in the study, had a second cancer that was not part of the study because it was likely a treatment-related cancer resulting from the effects of chemotherapy and/or radiation received for the initial cancer. These two diagnoses were unlikely to be relevant to this environmental investigation.

Cases were identified through the MDPH Massachusetts Cancer Registry (MCR) and, for more recently diagnosed cases (1998-2000), through Massachusetts hospital discharge records. Hospital discharge records were used because hospitals are given up to two years to report cancer diagnoses, and MDPH was interested in beginning data collection in 2002 before all cases may have been reported. All hospitals reporting childhood cancers to the MCR were contacted and asked to identify Wilmington cases diagnosed after 1997. The medical records of each reported case were reviewed to confirm that study inclusion criteria, as defined above, were met. MCR records in subsequent years confirmed that no cases were missed during the case recruitment process.

In accordance with standard MDPH study procedures, permission to contact and interview parents of cases was obtained from the diagnosing physician listed in the MCR record. A copy of the physician consent letter can be found in Appendix A. Once physician consent was obtained, study notification and recruitment letters were mailed to each case's parents. The letter introduced and outlined the scope of the investigation and assured complete protection of confidentiality (see Appendix A). The case recruitment letter was followed by a telephone call to obtain verbal consent to participate and to schedule an interview. The follow-up telephone call provided an opportunity to improve participation by attempting to address any questions or concerns the parents had about participation in the investigation. Up to 12 telephone calls were made at different times of the day and on different days of the week in an

attempt to reach parents before sending up to 2 additional follow-up letters. An additional 12 telephone attempts were made after each follow-up letter was mailed. Permission to participate was first sought from the case's mother or, if the mother was not the primary provider for the child, then permission was sought from the father or the most appropriate guardian. If a mother chose not to participate, she was asked for permission to speak with the father about participation. For refusals, MDPH evaluated the reason provided and determined whether or not follow-up was appropriate to further encourage participation. Cases were not enrolled if telephone contact was unsuccessful or if refusal to participate was obtained.

CONTROL DEFINITION AND ASCERTAINMENT

Controls were selected from among Wilmington children of the same age and sex as the cases. With the cooperation of Wilmington Public Schools, controls were identified from school rosters corresponding to the grades that cases were or would have been in during the 2001-2002 school year. For cases who were beyond high school age, controls were selected from Wilmington yearbook listings for the corresponding case graduation year. For cases that were not yet school-aged, controls were selected from Wilmington birth records for the year of the case's birth. Controls were randomly selected in order to minimize selection bias and to ensure that they were representative of the general population of Wilmington children. This was achieved by numbering each child in the corresponding grade or birth year using a random number generator to identify a pool of potential controls for each case. All school-aged controls, as well as all participating school-aged cases, attended public schools in Wilmington.

MDPH aimed to select four controls per case. Potential controls were recruited in the same manner as cases, including a series of recruitment letters and follow-up telephone calls (see Appendix A). To be eligible, a potential control was required to be a match on age (within one year) and sex for a participating case and to have lived in Wilmington during the same month and year of the case's cancer diagnosis. The residence requirement was determined by telephone contact after the initial study notification and recruitment letter was sent.

Controls who provided no response after three mailings and/or for whom telephone contact was unsuccessful were considered to have refused participation. However, if a mailing was returned by the post office due to an incorrect address then the control was considered ineligible.

ETIOLOGIC PERIOD

Two etiologic periods were evaluated in this study. First was the maternal exposure period, which represents *in-utero* exposure, and was defined as the period from one year prior to birth until the child's birthdate. Second was the childhood exposure period encompassing all of childhood from the month of birth to the date of diagnosis for each case or the reference date for each control (defined as their matched case's date of diagnosis).

DATA COLLECTION

A comprehensive structured interview was conducted with each participant from 2002-2004 (see Appendix B). Interviewers were trained and provided with an interviewer's manual to ensure consistency. Case recruitment ended in 2003, and control recruitment was completed in 2004. The majority of interviews (89%) were conducted in person at Tewksbury Hospital. One interview was conducted by telephone and the remaining interviews were conducted at the participant's home. An interview guide was mailed to the participant to be completed prior to the in-person interview with the purpose of facilitating recall and to be used as a reference during the interview. The interview guide listed types of birth defects and congenital malformations, sources of environmental exposures and chemicals, as well as participants' reference dates, residential history, medical history, and occupational histories (see Appendix B). Though some children were no longer considered minors at the time of the interview, all interviews were conducted with the mother or father of the child for consistency.

Interviews collected information on residential history; maternal characteristics such as alcohol use, smoking status, medical history, and reproductive history; child's medical history; child's daycare, school, and camp attendance history; recreational activity history for specific locations in Wilmington; occupational history for both the child (if applicable) and parents; and other possibly relevant household exposures.

CONFIDENTIALITY

All study participants provided informed consent to participate in this study. Consent was obtained by the parents. Medical record release was sought for all participants. All paper records were stored in a locked cabinet to which only study personnel had access. Electronic records were encrypted and password protected. Only study personnel had access to the electronic interview data and analytic files.

EXPOSURE ASSESSMENT

This study was designed to be exploratory in nature with the purpose of identifying possible differences between cases and controls with respect to a variety of potential environmental exposures. The exploratory design was implemented because of no clear *a priori* knowledge of common factors or environmental exposures that were thought to be relevant to childhood cancer in Wilmington. However, when NDMA was detected in water supply wells in 2003, the primary focus of the investigation was re-centered around potential exposure to NDMA-contaminated drinking water and, therefore, a comprehensive retrospective exposure assessment was conducted. It was later determined, in part through the peer review process, that assessment of trichloroethylene (TCE) exposure was also necessary to sufficiently evaluate the association between childhood cancer in Wilmington and potential environmental factors.

N-Nitrosodimethylamine (NDMA)

There were no NDMA data available for any wells during the time period of interest for this study (1974-2000). Thus, groundwater and water distribution system modeling was necessary to estimate possible concentrations of NDMA in residential drinking water during the time period of interest.

The goal of the NDMA exposure assessment was to reconstruct the concentration history of NDMA in the Wilmington public drinking water distribution system between 1974 and 2000. To meet this goal, the following steps were carried out:

Record review: Documents were obtained on the history of manufacturing and waste disposal activities at the Olin Chemical site; on the underlying bedrock and hydrology of the site; and on historical water quality data. The Wilmington Water and Sewer Division, the US EPA, and MA DEP provided this information to understand pollutant sources and their fate and transport from the Olin Chemical hazardous waste site and within the Maple Meadow Brook (MMB) aquifer;

Groundwater modeling: A groundwater flow and contaminant fate and transport model was developed to estimate pollutant concentrations in the aquifer along with travel times from source locations to drinking water wellheads;

Drinking water distribution system model: A public drinking water distribution system model was developed to estimate pollutant concentrations in individual water supply mains throughout Wilmington for each month from 1974-2000; and

Study participant exposure estimation: Average monthly concentrations of NDMA were estimated at each residential address for each study participant.

Details on the groundwater and water distribution system models can be found in Appendix C.

Record Review
Review of historical documents on the manufacturing and waste disposal activities at the Olin Chemical site included the Comprehensive Site Investigation report (CRA 1993), the Supplemental Phase II Report (Smith 1997), and the Phase II Comprehensive Response Action Status Report (MACTEC 2003a). Products used and produced at the site were identified, along with a timeline of their use and other site activities. While NDMA was not found to be manufactured or used at the Olin Chemical site, NDMA precursor compounds (such as various nitrogenous products like nitrite and ammonia) as well as other *n*-nitrosamines were produced from 1953-1986 and disposed of on site. The exact process or processes by which NDMA was formed at the site is not known. However, based on the kinetics of NDMA formation by nitrosation, the NDMA was likely formed on site soon after precursor compounds were dumped (likely within hours or days of disposal). The historical records of chemical manufacturing and disposal suggest that disposal of NDMA precursor wastes into unlined pits began by 1956 or earlier and increased until 1970, when disposal was then directed into the sewer system (CRA 1993). Wastes were also disposed into onsite septic tanks with onsite leaching fields (MACTEC 2003a).

Until 2003, no NDMA testing of the water system had been conducted—neither the wells, the raw water entering the treatment plant, nor the finished water leaving the treatment plant. The measurement of major DAPL ions such as sodium were used to test, and ultimately support, the hypothesis that NDMA found in the water system originated from the DAPL. For example, the coefficient of correlation (r) for sodium and NDMA in groundwater samples was 90%. Levels of NDMA detected in contaminated wells in 2003 were between 30 and 170 ng/L. No NDMA was detected in the finished drinking water at the time of well sampling, most likely because the contaminated wells were closed in 2003 prior to the time of sampling the finished drinking water.

Groundwater Models
Since no NDMA measurement data exists prior to 2003 for the Butters Row municipal water supply wells, groundwater flow and contaminant fate and transport models were necessary to estimate NDMA concentrations reaching the wells. A groundwater plume model had been previously developed by Olin's contractors (i.e., Geomega, MACTEC, GEI Consultants, etc.) for areas adjacent to the Olin Chemical site; the model integrated

sampling data, historical records, and fate/transport models. The model developed for this study was based in large part on the ground water flow model originally described in Geomega (2001a), and later revised in Geomega (2006). Utilizing the previous modeling, along with historical records of chemical manufacturing at the Olin Chemical site and records of the Wilmington water supply well characteristics (e.g., pumping and discharge rates) for the 1956-2003 period, MDPH contractors modeled the transport of the plume of NDMA in the groundwater between 1956 and 2003. By reconstructing the concentration history of NDMA throughout the MMB aquifer, the groundwater models enabled estimation of when NDMA first arrived at the water supply wells and how NDMA concentrations changed over time in individual wells. The US Geological Survey's (USGS) numerical finite-difference code, MODFLOW (McDonald and Harbaugh 1988), was used to simulate groundwater flow conditions, and MT3D (Zheng 1990) was used for simulation of NDMA transport.

The groundwater model simulations estimate that NDMA reached the Chestnut St. #1 well in 1974 and the Butters Row #1 well in 1981. These two wells contained the highest NDMA concentrations ranging from approximately 50 to 250 ng/L. Both Butters Row #2 and Chestnut St. #1A/2 wells contained lower levels of NDMA and were contaminated for shorter periods of time relative to the Butters Row #1 and Chestnut St. #1 wells. Measurements indicate that NDMA did not reach the Town Park well, which was located farther to the north in the MMB aquifer relative to the other wells.

Additional details of the groundwater flow and contaminant fate and transport models (including model calibration and validation) can be found in Appendix C.

Water Distribution System Model
In addition to the groundwater transport model, DPH contractors developed a water distribution system model to estimate pollutant concentrations in individual water supply mains throughout the town's public drinking water system. First, results of the groundwater models were used to specify monthly concentrations of NDMA at the supply wells and the Butters Row Water Treatment Plant (WTP). Then, the water distribution system model was used to estimate how concentrations would vary across the town's water mains as water entered the system directly from supply wells and from both the Sargent WTP in the north and the Butters Row WTP in the south. Over the course of the study period, different supply wells and WTPs were active, inactive, not yet online, or temporarily offline. The model inputs accounted for these changes over time and simulated how the water mixed together within the network of water supply mains of the distribution system for every month from January 1974 to December 2000. Finally, these estimates were used to assign monthly concentrations at each participant's residential water supply main.

It is estimated that very little NDMA would have been removed by treatment at the Butters Row WTP due to the physical/chemical properties of NDMA (US EPA 2012) and the nature of the treatment systems in use. In short, the main processes in operation and potentially capable of impacting NDMA levels were aeration, photolysis, and sorption onto activated carbon. However, NDMA is relatively non-sorptive for activated carbon and not readily volatilized from water, making aeration ineffective, as well. In addition, the sedimentation tanks at the Butters Row WTP were 13 feet deep, the hydraulic residence time only 100 minutes, and sunlight was filtered through glass ceiling panels, making it unlikely that direct photodegradation of NDMA would have occurred. Thus, for purposes of the water distribution system model estimates, it was assumed that concentrations in the wells would be the same as concentrations in the water leaving the Butters Row WTP. For additional details regarding the estimation of NDMA removal during water treatment, please see Appendix C.

Using the commercially available software application, WaterCAD, a hydraulic model of the Wilmington water distribution system was developed to simulate the spatial distribution of NDMA within the town's water network. Annual models of the system were created for each year from 1974 to 1989 and for every other year from 1990 to 2000, so that differences in the water distribution system and pumping patterns could be accounted for over time. Information on the construction of new pipes over this period were obtained from various reports carried out for the Wilmington Water and Sewer Division, historical logs of system improvements reported in the town's annual reports, assessor's maps, and road maps.

The spatial penetration of NDMA into the town drinking water system was found to primarily depend on the proportion of water entering the distribution system from the contaminated MMB aquifer supply wells and the Butters Row WTP compared to the proportion coming from the uncontaminated northern water supply wells and Sargent WTP. The relative proportions of water entering the system from each location depended on the overall town water demand and pumping rates, which frequently changed. The magnitude of NDMA concentrations in the distribution system strongly depended on the concentrations of NDMA in the MMB aquifer source wells and the Butters Row WTP. The contaminant distribution also depended to a lesser extent on the water demands of industrial and commercial users relative to domestic users, and on the pipe network configuration, which varied over the simulation period.

Based on the water distribution system model results, simulated NDMA concentrations steadily increased from 1974 (when initial contamination of the Chestnut St. #1 well is estimated to have occurred) to June 1979. The extent of NDMA within the system, however, was less extensive than in later years with 31% of all pipes exceeding 1 ng/L

and just 12% exceeding 50 ng/L. From July 1979 to May 1981, all wells in the MMB aquifer had been deactivated except for Town Park, which was not contaminated with NDMA. However, when the Butters Row WTP was brought online in June 1981, NDMA concentrations rapidly increased. From 1981 through 2000, the spatial extent and magnitude of NDMA in the system varied widely from month to month, with the monthly mean and maximum concentrations computed across all pipes ranging from 5 – 39 ng/L and 12 – 114 ng/L, respectively. The percent of all pipes in the system with concentrations exceeding 50 ng/L reached a peak of 63% in November 1991. In March 1998, 27% of all pipes had concentrations exceeding 100 ng/L. NDMA exposure was primarily limited to the southern, central and western areas of town; exposure in the northern and eastern areas was relatively low because those areas primarily received water from uncontaminated sources (i.e., the northern water supply wells and Sargent WTP).

Simulated water distribution system concentrations of NDMA for a selection of years are presented in **Error! Reference source not found.** These illustrate the variability o f NDMA concentrations across the water distribution system and over time.

Figure 5. Average annual simulated NDMA concentrations in water mains of the Wilmington public drinking water distribution system for select years from 1975 to 2000.
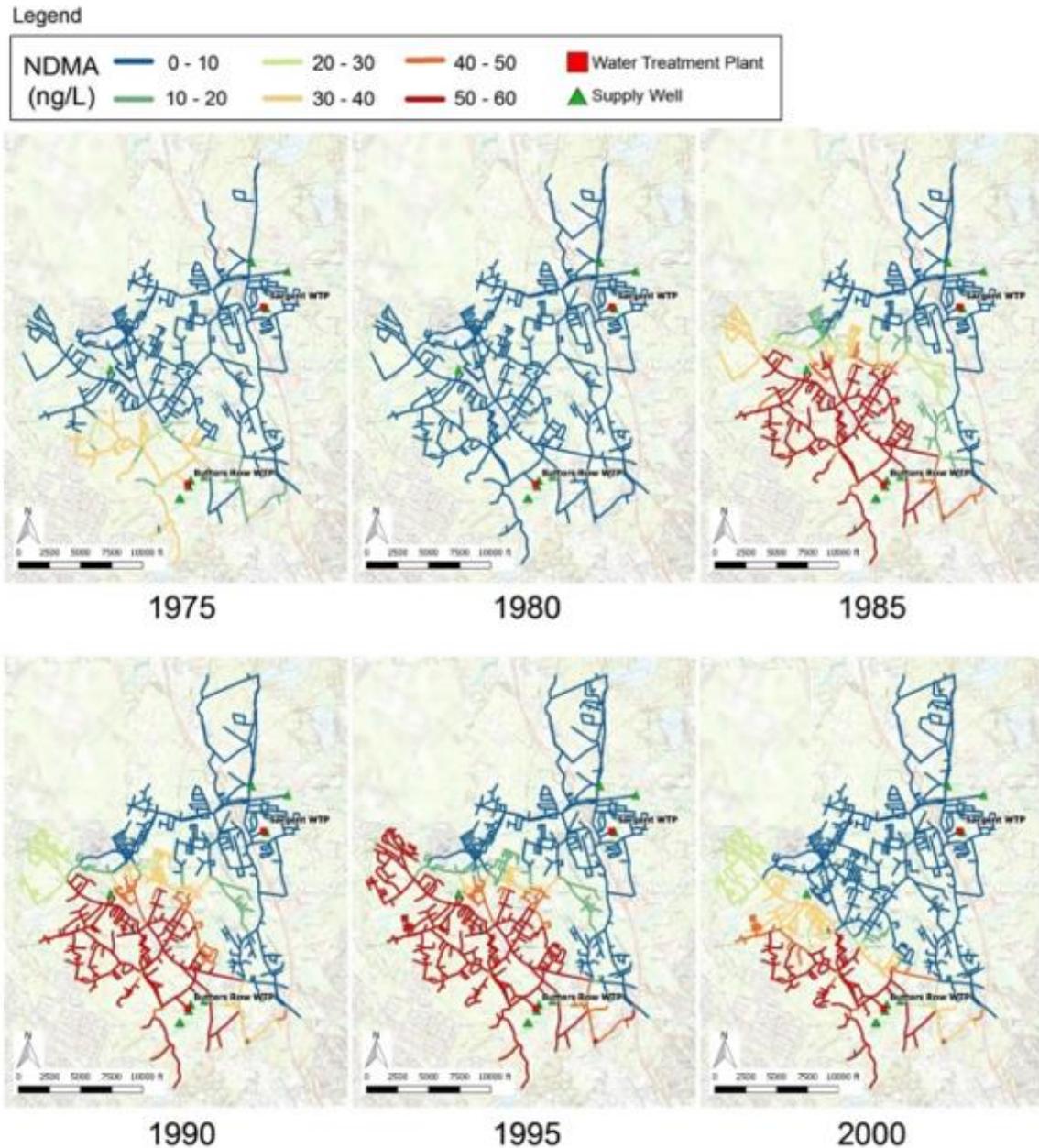
Source: Durant et al., 2018. Modeling *N*-Nitrosodimethylamine and Trichloroethylene Concentrations In The Wilmington, Massachusetts, Water Supply System: 1974 To 2000. Available as: Appendix C, Figure 5.33.

The modeling of NDMA concentrations for this study does not address the possible formation of NDMA within the water distribution system itself. However, based on records of the water chemistry and water disinfection practices at the Butters Row WTP, it is unlikely that formation of significant concentrations of NDMA—as a disinfection byproduct—occurred within the drinking water distribution system. The Butters Row WTP used chlorination (chlorine gas) as the primary type of drinking water disinfectant, as opposed to chloramination. NDMA can be a byproduct from chlorination in the presence of other necessary precursors; however, based on available information, there was no evidence of NDMA formation within the water distribution system in Wilmington (see Appendix C for more detail). As noted previously, NDMA has never been detected in the Wilmington water distribution system. Testing for NDMA took place only after the water supply wells previously found to have been contaminated with NDMA had been shut off for several months. Likewise, there was no evidence of NDMA precursor chemicals—most importantly dimethylamine—in the water distribution system.

Model Sensitivity and Uncertainty

Sensitivity analyses were performed to evaluate the impact of alternative model configurations, parameters, and input datasets on model results. For the groundwater flow model, the sensitivities to alternative spatial discretization, simulation time step durations, and various hydraulic parameters were evaluated by comparing changes in the simulated potentiometric head at monitoring well locations near the MMB aquifer wells. The sensitivity of the water distribution model to diurnal variability in water demands was also evaluated. See Appendix C for more details.

To evaluate the impact of uncertainty on the final output of the NDMA exposure assessment modeling, a review was conducted of the relative uncertainty and sensitivity of all model assumptions, parameters and input datasets. Those parameters and inputs for which the model sensitivity was known to be low (i.e., large changes in the parameter or input value did not cause large changes in the output) were removed from consideration as were any parameters that were adjusted during model calibration. Input datasets that were based on relatively complete historical records or believed to be reasonably accurate were also excluded. Ultimately, two model inputs were identified for which relatively high uncertainty exists and which were found to cause significant impact on the model results: the arrival time of DAPL to the Western Bedrock Valley in the MMB aquifer and the pumping rates for supply wells during the period when pumping data were most limited.

For each of these inputs, the highest and lowest most likely values were estimated based on available information (DAPL arrival +/- 5 years and pumping rates +/- 20%). Then

the entire dataset of monthly NDMA concentrations for locations throughout the distribution system were reproduced for each variation of the two parameters, providing uncertainty ranges of monthly NDMA concentrations for each pipe in the distribution system. These datasets (eight in all) were later incorporated into exposure-outcome analyses to evaluate the impact of these uncertainties on final epidemiologic results.

Trichloroethylene (TCE)

As with NDMA, the goal of the exposure assessment was to reconstruct the concentration history of TCE in the Wilmington water distribution system. Unlike NDMA, the period of potential exposure to TCE was believed to be much narrower. Another important difference is that historical TCE measurements in finished drinking water were available directly from the Wilmington Water and Sewer Division, which began measuring chlorinated volatile organic compounds, including TCE, in 1979 following the discovery of contamination of municipal wells in nearby Woburn, MA. Therefore, TCE concentrations in the water distribution system were based on historical water testing data as opposed to groundwater modeling results. Unlike NDMA, water distribution system sampling data were available, although limited. Also, the sources of TCE contamination were insufficiently characterized to enable groundwater transport modeling. For these reasons, estimation of TCE concentrations in the water distribution system were limited to years in which sampling data were available (1981-2000), even though it is known that contamination was present before that time.

Water Distribution System Model
A re-constructed time history of monthly TCE concentrations in the Butters Row WTP finished water was generated for 1981 through 2000. Data from individual wells were either not available or very limited prior to 1981, and therefore the TCE simulation corresponded to the period when the Butters Row WTP was online (June 1981 through December 2000). Concentrations at the supply wells outside the MMB aquifer and at the Sargent WTP were assumed to be zero, making Butters Row WTP the sole source of TCE to the system.

To re-construct a monthly time history of TCE, the mean concentration was first computed for each month in which two or more samples were collected. Non-detects were set to the reported detection limit (i.e., 0-1 μg/L). For months in which no samples were collected, the concentration was estimated by linearly interpolating between the mean concentrations of the closest two months for which measurements were available. The result was a time series of monthly mean TCE concentrations.

The water distribution system model previously described was applied. The results showed that TCE concentrations were highest from 1983 through 1987, reaching a

maximum monthly average of 26 µg/L in August 1985. In 1987, the concentrations fell rapidly and were consistently below the detection limit starting in 1991. The highest levels corresponded to high levels observed at the Butters Row WTP. Similarly to what was observed with NDMA, higher concentrations occurred in locations near the Butters Row WTP within the southern, central, and western areas of town (Figure 6). When TCE levels at Butters Row WTP were the highest, it is estimated that 60% of all water mains in the town had concentrations exceeding 20 µg/L. From 1990 through 2000, TCE levels were below detection limits at the WTP and across the system. Figure 6 shows examples of how TCE concentrations varied geographically and over time. As with NDMA, the variability is a reflection of the changing concentration of TCE in the system over time and the variability in municipal well pumping over time.

Figure 6. Average annual simulated TCE concentrations in water mains of the Wilmington public drinking water distribution system for select years from 1981 to 1989

1981

1983

1985

1987

1989
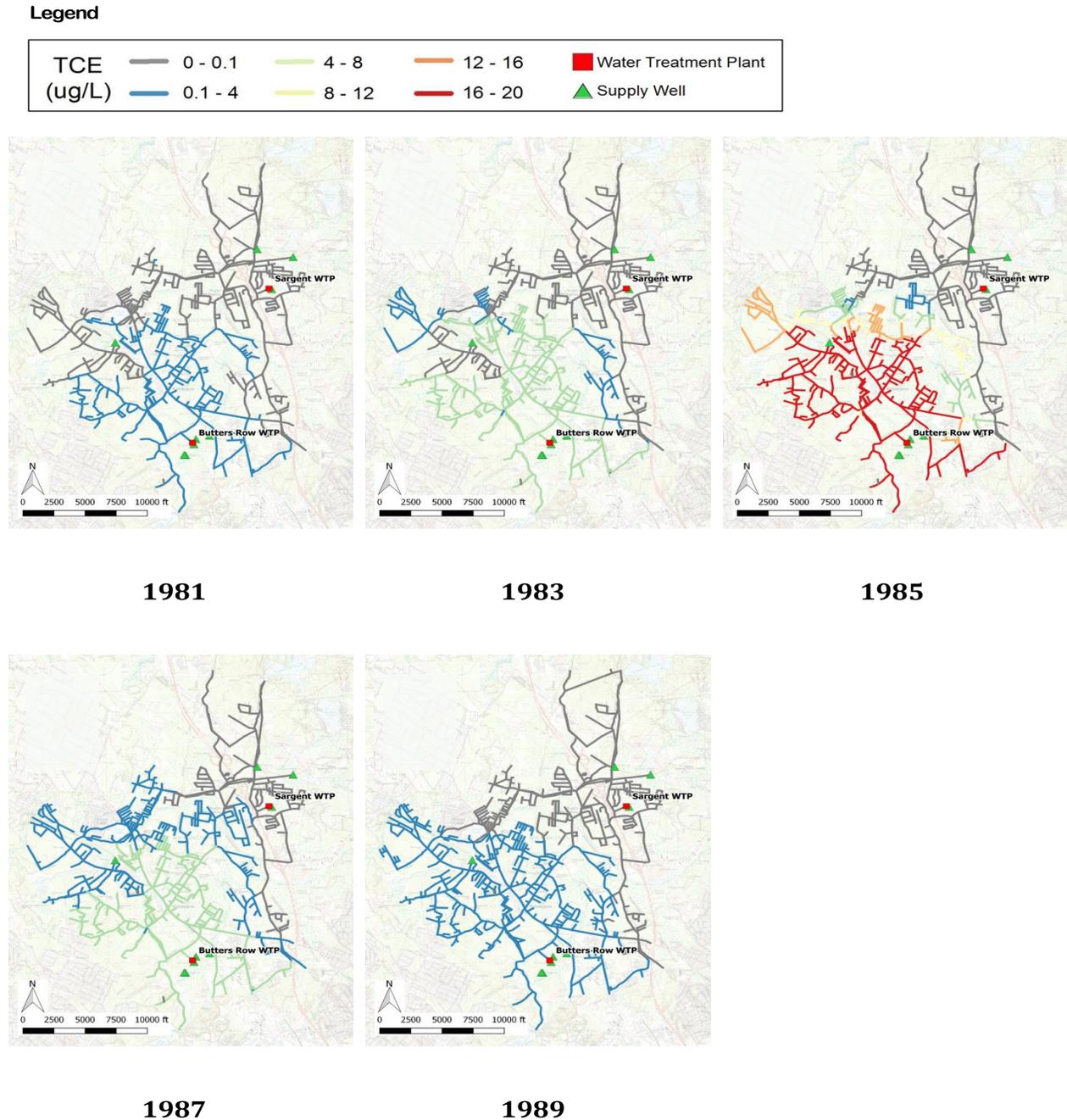
Note: The MCL for TCE is 5 ug/L.

Source: Durant et al., 2018. Modeling *N*-Nitrosodimethylamine And Trichloroethylene Concentrations In The Wilmington, Massachusetts, Water Supply System: 1974 To 2000. Available as: Appendix C, Figure 5.37.

Geocoding and Monthly Mean Residential Concentration Assignments

Using the water distribution system model, average monthly estimates of NDMA concentration (ng/L) were generated from January 1974 through December 2000 and average monthly estimates of TCE concentration (μg/L) were generated from June 1981 through December 2000 for all water mains in the water distribution system. To estimate the average NDMA or TCE concentration at a specific address for a specific month, the closest water supply main to that address was determined using ArcGIS software.

All street addresses from the residential histories of cases and controls were geocoded using ESRI's ArcMap software (ESRI v. 9.3.1). The address locator used was type 'US Streets with Zone', with the zone being an internal Massachusetts town code and Tele Atlas' Dynamap product, January 2010 version, as the reference dataset. The locator was set to accept only match scores of 100, tied candidates were not mapped, and a side offset of 10 meters was used. Addresses that did not map automatically (~5%) were manually mapped using publicly available resources including the United States Postal Service website and Google Maps. To ensure accuracy, manually mapped locations were later adjusted as needed using assessor's parcel data for Wilmington from MassGIS.

The Wilmington water main system was initially developed as a digitized version of the town's Water Works Facilities Master Plan (FST 1988) and was then updated with supplemental water main information provided by the Wilmington Water and Sewer Department for subsequent years not covered by the 1988 master plan (see Appendix C for additional detail). Created as an ESRI shapefile, the water main system was linked to the geocoded street addresses using the 'Near' tool in ArcInfo, which generated distances to nearby water supply mains for each residential address. Each residence was then assigned the water supply main that was the shortest distance away. Lastly, a visual inspection was performed to verify that each residence was assigned the proper water main, and corrections were made as needed. All geocoding and water main assignments, including manual adjustments, were conducted by staff who were blinded as to the case/control affiliation of the addresses.

Missing Exposure Data

Many study mothers moved to Wilmington only after their child was born, and a number of participants moved in and out of the town of Wilmington during childhood. It was assumed that no exposure to NDMA or TCE was experienced during months lived outside of Wilmington.

Some study residences were not connected to the Wilmington public drinking water system and used a private well for drinking water. Interview responses regarding home drinking water source were used to identify private well use, and the Wilmington Water and Sewer Division confirmed the lack of connection to town water for each location during the period reported. There were 10 study participants whose home drinking water came from a private well for at least one month during either the maternal or childhood exposure periods. To assess the potential for direct contamination of the private wells by NDMA, MDPH used results of historical well monitoring done by Olin Corporation from 1990 to 2005 and those of private well sampling offered by EPA starting in 2008 along with a map of the approximate limit of groundwater impacts outlined by US EPA using data from MACTEC's Draft Focused Remedial Investigation Report (MACTEC 2007). None of the addresses were within the NDMA impact area and sampling results indicated that the NDMA plume had not reached as far south and west as even the closest addresses to the vicinity of groundwater impacts. Therefore, no study participants were determined to have the opportunity for exposure to NDMA through their private well.

No assumptions could be made for potential exposure to TCE through private well water because the source of TCE contamination was unknown and, therefore, no groundwater modeling was possible. Similarly, a number of participants lived in Wilmington during the period when TCE was known to be present in the town's water distribution system, but prior to the time when TCE measurement data was available. For these reasons, a number of study participants were excluded from the TCE portion of analysis. Fifteen (15) children had missing maternal period exposure data and 24 had missing childhood period exposure data. Due to the matched study design, the exclusion of these participants forced the exclusion of additional matched controls and, sometimes, matched cases. In total, 19 children were excluded from the TCE analysis for the maternal exposure period and 34 children were excluded from the TCE analysis for the childhood exposure period. Two children with only one month of missing data were not excluded. One child was missing only 1 month of childhood period TCE data for the time before TCE estimates were available, and this was followed by many months of estimated TCE concentrations of 0 μg/L. This child's missing month of data was set to a concentration of 0. Another child was missing only 1 month of maternal period TCE data due to the use of a private well in 1997 during the month before the child's birth. This child's missing month of data was also set to a concentration of 0.

STATISTICAL ANALYSES

All data were collected as dichotomous (e.g., yes/no) or categories of responses (e.g., 0 years/1-5 years/ 6-10 years), except for the monthly modeled water contaminant

concentration data, which were provided on a continuous scale. Analyses included simple descriptive (i.e., numbers used to describe or summarize a variable) and inferential statistics (numbers used to test a hypothesis) using univariate (one variable described, like the number of females and males), bivariate (two variables compared, like low birth weight and case/control status), and multivariate methods to evaluate the association between childhood cancer and various risk factors, including potential exposure to NDMA or TCE in drinking water. All analyses were conducted and presented for the total study population, called the All Cancers group, and for the Leukemia/Lymphoma subgroup, comprised of all the leukemia and lymphoma cases and their matched controls. The leukemia and lymphoma cases were analyzed together because there is some evidence that these cancer types may share a more similar etiology compared to all types of cancer combined.

Statistical analyses were performed using SAS statistical software version 9.3 (SAS 2010). A matched case-control design was selected in order to increase statistical efficiency (i.e., stability of the odds ratios) due to the relatively small number of cases. Multiple controls were selected for each case to further increase efficiency (Schlesselman 1982; Miettinen 1969).

NDMA and TCE Exposure Metrics

Modeled concentrations of NDMA and TCE in drinking water mains at residential addresses were used as a surrogate for potential exposure. The estimated average of all non-zero monthly concentrations of NDMA was used as the measure of exposure to NDMA. The estimated average of all non-zero monthly concentrations of TCE was used as the measure of exposure to TCE. Table 4 provides details of these exposure metrics.

 An alternative exposure metric was explored in which all months of NDMA or TCE concentration estimates were averaged, including months estimated as zero. The zero-inclusive metrics were highly correlated with those used and described in Table 4(Pearson correlation coefficient (r) = 0.99 and 0.88 for maternal and childhood exposures, respectively). The metric selected was chosen as it best describes the actual concentrations to which study participants were likely exposed. While it does not account for duration of exposure within the metric itself, duration was also evaluated and included in exposure-outcome models.

Table 4. NDMA and TCE Exposure Metrics Used for Data Analysis

Exposure Metric	Description	Time Period Definition
Maternal average concentration	Average of all non-zero monthly concentration values estimated in residential drinking water	12 months prior to the child's birth month
Childhood average concentration	Average of all non-zero monthly concentration values estimated in residential drinking water	child's month of birth to the month of diagnosis (cases) or reference date (controls)

Analyses of NDMA and TCE exposure were conducted as dichotomous (ever/never) and as categorical (zero/low/high). The latter allows for an assessment of a dose-response relationship. Categorization of exposure as 'never' means that modeled concentrations of NDMA or TCE were zero for all months of residence for the etiologic period of interest (i.e. maternal or childhood). For the 'zero/low/high' categorization, the 'zero' exposure group is identical to the 'never' category, while the remaining participants are divided into 'low' and 'high' categories based on the median of the remaining participants' (the 'ever' group's) average monthly concentrations. The low/high cut point was based on the entire 'ever' exposed study population and was re-calculated for all sub-analyses to reflect the median average monthly concentration of the participants in the sub-analysis being conducted (e.g. the Leukemia/Lymphoma subgroup analysis).

Adjustment of Water Intake

Due to limitations in the questionnaire design, detailed exposure calculations incorporating each person's daily water intake were not conducted. However, participants were asked whether their primary drinking water source for a particular residence was tap water, filtered tap water, or bottled water and additional analyses were conducted to evaluate potential exposure while accounting for bottled water usage during the maternal exposure period. Water filtration is not thought to have been a relevant factor since, according to the WHO, NDMA is not removable by methods available for home filtration including activated carbon adsorption, air stripping, reverse osmosis, or low-powered UV light (high-powered UV treatment is thought to be potentially effective) (WHO 2017).

Maternal bottled water usage was accounted for in potential exposure estimations using two different methods. In one analysis (Method A), mothers who responded that they primarily drank bottled water while living at a particular residence were assigned an NDMA or TCE concentration of zero while living in that location. In the other analysis (Method B), NDMA or TCE concentrations were reduced to 49% of modeled values for the months in which a mother reported that they primarily drank bottled water.

Children's water intake was complicated by several factors that prevented adequate incorporation of intake information into exposure estimates. Parents were asked to report whether their child was breastfed, for how long they were breastfed, and whether they were given formula during the first year. Unfortunately, they were not asked whether the child was exclusively breastfed or how much formula was given and 84% of breastfed children were also given formula during the first year, with half reporting the formula was at least sometimes made with tap water. Furthermore, questions regarding daily intake of tap water were only asked once per address during the residential history interview and, thus, changes in water intake over time were not adequately captured for children, particularly those who lived in one home for many years spanning infancy, childhood, and adolescence. For these reasons, water intake information was not incorporated into any childhood exposure analyses.

Analytic Tools

The principal statistic used to interpret the analytic results was an odds ratio (OR) for matched cases and controls produced using conditional logistic regression. This method predicts the outcome (e.g., risk of childhood cancer) based on one or more predictor variables (e.g., NDMA exposure). To appropriately account for matching criteria, the SAS procedure PROC LOGISTIC and the STRATA option were applied.

An odds ratio is a measure of association between a health outcome and an exposure or risk factor. In general, an odds ratio is calculated as the odds of an exposed population developing a particular health outcome compared to the odds of an equivalent but *un*exposed population developing the health outcome. As presented in Table 5, the calculation would be a/c divided by b/d, where the letters represent the number of study participants in each category. In a matched study design, however, the calculation is simplified because only matched pairs with a different exposure status (called "discordant pairs") provide useful information. The calculation for a matched odds ratio, such as in this study, is the number of "a,d" pairs divided by the number of "b,c" pairs (see Table 5).

Table 5. Case-control contingency table with matched pair possibilities

	Exposed	Not Exposed	Concordant Pairs	Discordant Pairs
Cases	a	b	a,c	a,d
Controls	c	d	b,d	b,c

An odds ratio of 1.0 means that exposure is not related to the outcome. A value greater than 1.0 means that exposure has a positive association with the outcome. A value less

than 1.0 means exposure has a negative association with outcome. Therefore, as an example, an odds ratio of 2.5 means that the odds of an outcome occurring is 2.5 times higher than if there were no exposure.

For all odds ratios, 95% confidence intervals were calculated. A confidence interval (CI) measures how reliable the odds ratio is and provides a range of values within which the point estimate will fall 95% of the time given an unbiased sample and analysis. A CI that includes 1.0 means that the association is not statistically significant and may be due to chance, even if the OR estimate is much higher than 1.0. If the CI excludes 1.0, then the association can be considered statistically significant. A wide confidence interval that excludes 1.0 indicates that the association is statistically significant, but that the precise strength of the association is not clear.

A *p*-value is a related measure, which describes the statistical significance of an odds ratio or other effect estimate. The larger a *p*-value, the less precise the OR is. A *p*-value <0.05 is generally considered to be statistically significant. However, importantly, a large *p*-value does not mean that the result is invalid. It may indicate that insufficient information is available to adequately evaluate the result, commonly due to small sample sizes.

The potential for statistical confounding was evaluated using univariate analyses for matched cases and controls. The variables evaluated were those identified prior to the start of the study as potential risk factors for childhood cancer. Any variable with a univariate odds ratio result >1.0 and a *p*-value <0.20 for the association with all cancers or with leukemia/lymphoma was evaluated as a possible confounder. Logistic regression models were run with these possible confounders individually to determine if the variable had an impact on the main effect estimates of NDMA or TCE exposure. A variable was considered to be acting as a confounder if the effect estimates for exposure changed by at least 10% when the covariate was included in the model. Confounding was evaluated in models of association between both the All Cancers group and the Leukemia/Lymphoma sub-group for maternal and childhood NDMA exposure measured as dichotomous (ever/never) and as categorical (zero/low/high) average modeled NDMA concentrations in drinking water. Due to sample size considerations, TCE exposure analyses were evaluated for confounding only among the All Cancers group and only using dichotomous (ever/never) modeled TCE concentrations; however, confounding was evaluated for both maternal and childhood drinking water models. Due to sample size limitations, it was not possible to include multiple confounders in the same model.

Tests of trend for categorical exposure variables were evaluated by assigning the median concentration value of each category to study participants in that category. The resulting exposure variables were then treated as continuous variables while assessing associations with the outcome in conditional logistic regression analyses.

Statistical Inference

Odds ratios are presented with 95% confidence intervals along with either *p*-values or notation to indicate statistical significance (i.e. *p*-value <0.05). ORs with a *p*-value <0.10 (but ≥0.05) are considered marginally significant and are noted in the text and tables. As previously explained, ORs provide a point estimate of the association between a risk factor and childhood cancer while confidence intervals help to understand the reliability of the OR. Statistical significance is presented and used in this study as a tool to help identify potentially meaningful results. However, statistical significance is not the only criteria used to interpret results and draw conclusions; results that are not statistically significant may still be considered relevant to the conclusions. Careful consideration of the following contributed to all study conclusions:

- The magnitude of ORs
- The width of CIs
- *P*-values
- The presence or absence of dose-response trends
- The presence of consistency in the results
- The plausibility of an association based on the scientific literature
- The presence and potential impact of any confounding, measurement error, or bias.

PEER REVIEW

Following completion of the exposure assessment and data analysis in 2014, a detailed study report of methods, results, and conclusions was submitted to an independent peer review committee. The purpose of the peer review was to ensure that the methodology applied was scientifically valid and that the conclusions reached were justified by both the methods used and results generated. The peer review committee was comprised of three scientists, one with expertise in childhood cancer, one with expertise in NDMA, and a third with expertise in water modeling.

The peer review committee suggested conducting additional analytical work related to the exposure assessment of NDMA to validate analytic assumptions of key model parameters and to better evaluate uncertainty in the modeling. The committee also

recommended more work to evaluate the potential role of TCE in the town's drinking water. MDPH believed it was necessary to address the reviewers' comments before considering the study complete. After additional review of historical records including a more detailed assessment of industrial water usage, new groundwater modeling was conducted in 2015-2017. The new modeling included monthly concentration estimates for TCE, uncertainty evaluation of key model parameters, and sensitivity analyses of the results (see Appendix C for details). Subsequent epidemiologic analyses were completed in 2018 and a final peer review was conducted prior to study release in 2019.

RESULTS

PARTICIPATION RATES

Case Participation

Figure 7 details the case recruitment and participation of the 22 children (23 cancer diagnoses) reported to the MCR between 1990 and 2000. The number of diagnoses was greater than the number of children because one child was reported to the MCR as having two primary site cancers diagnosed approximately five years apart. The second cancer was possibly a treatment-induced cancer (AML) secondary to the first cancer (bone). This child was recruited as a case, but only relative to their first primary cancer (bone). The possibly treatment-induced cancer was not included in the study. In keeping with the study's case definition, one child with a diagnosis of melanoma was also excluded from the study.

Physicians for 20 of the 21 eligible children provided permission for study recruitment. One family did not respond to recruitment attempts and one refused enrollment. The remaining 18 case children were enrolled in the study, resulting in a participation rate of 86% (see Figure 7). Residential histories were unavailable for any of the non-participating cases and, therefore, an evaluation of the potential for exposure to contaminants in drinking water was not possible for non-participating cases.

Figure 7. Recruitment and participation among 22 Wilmington childhood cancer cases
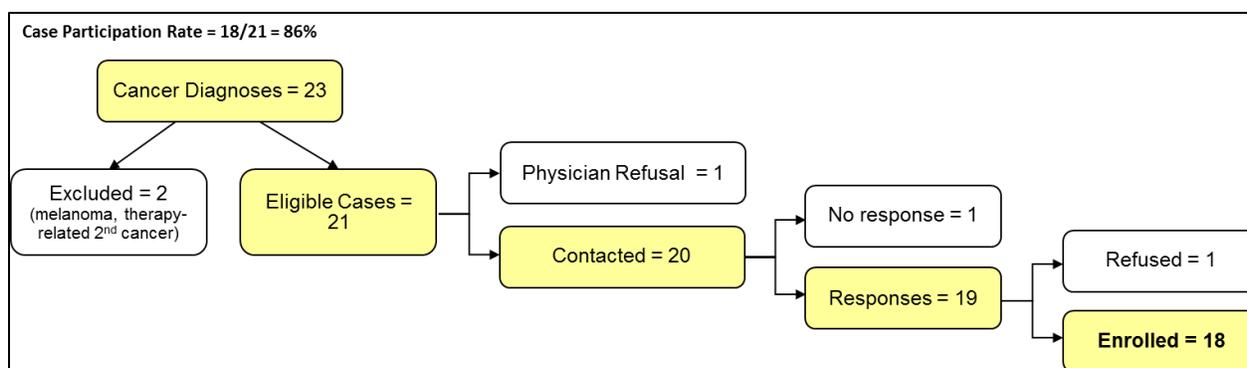
(23 diagnoses), 1990-2000

Control Participation

A total of 305 controls were contacted for possible participation in the study. Of these, 73 were found to be ineligible due to an incorrect address, failure to match a case on age

and sex, not being a resident in Wilmington during the matching case's diagnosis date, or, in one instance, Wilmington residency prior to 1974 which prevented accurate exposure assessment. An additional 118 did not respond to any of the three mailings and 40 refused to participate. In total, 74 controls were enrolled and matched with the 18 participating cases for a control participation rate of 32% (see Figure 8). The recruitment and participation of controls for the Leukemia/Lymphoma subgroup followed a similar pattern with 172 potential controls, 139 eligible controls, and 45 enrolled for a participation rate of 32%.

Figure 8. Recruitment and participation of 305 potential controls for the Wilmington Childhood Cancer Study, 1990-2000

Control Participation Rate = 74/232 = 32%
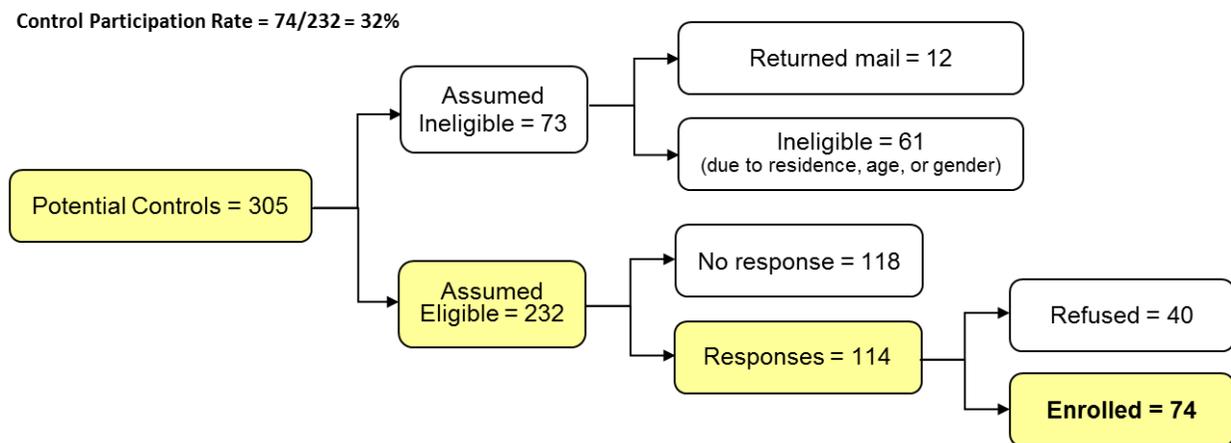
Since residential location may be related to exposure, the geographic distribution of addresses for non-participating controls was compared to that of participating controls to identify differences that might suggestion the presence of participation bias. The distribution of addresses of both groups was similar with respect to the proportion of each within the southern/southwest section of Wilmington receiving the higher concentrations of n-nitrosodimethylamine (NDMA) and trichloroethylene (TCE) (red/orange sections of town in

Figure 5 and Figure 6) and the northern/northeast section of town, estimated to receive very little of the contaminants (green/blue sections of town in

Figure 5 and Figure 6). Of 94 eligible controls in the southern/southwest section of Wilmington, 34% participated, and of 134 eligible controls in the northern/northeast section of Wilmington, 31% participated. This suggests that control participation was likely not related to the opportunity for exposure to drinking water contaminants. However, only current addresses were available for non-participating controls (not full residential histories) so a detailed assessment of drinking water contaminant exposure was not possible for those controls who did not participate.

The average number of matched controls per case was 4.1, matching the original study design goal. The number of matched controls ranged from three to six per case, with only three cases having less than four (see Figure 9). The case:control ratio for the Leukemia/Lymphoma subgroup was similar at 4.1 with one case having three controls and two cases having five controls.

Figure 9. Case:Control Ratio for the Wilmington Childhood Cancer Study, 1990-2000
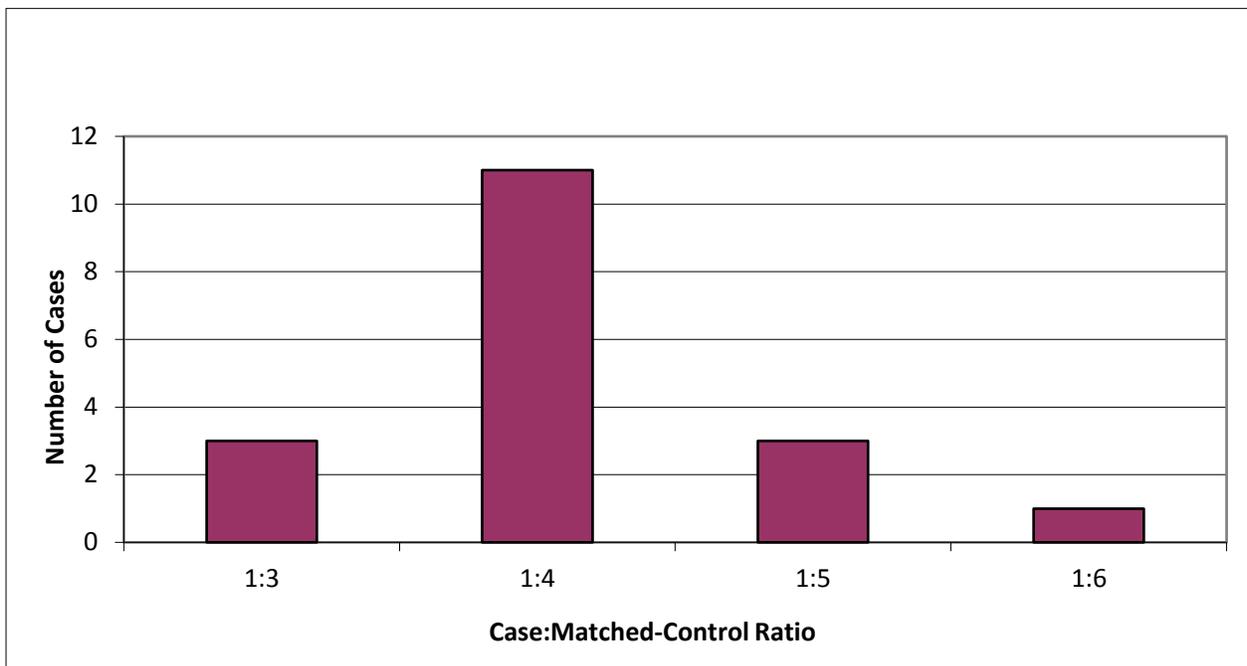
Characteristics of Participating and Non-participating Cases

Table 6 presents characteristics of the 18 childhood cancer cases enrolled in the study and the 3 cases that did not participate. Twelve out of the eighteen enrolled cases were male (67%). The age range of enrolled children diagnosed with cancer was between 1-19 years, with 7 children (39%) diagnosed at the age of four years or less. The mean age at diagnosis for participating cases was 8.8 years. Of the three cases not enrolled, one was

male and two were female; two were in the 10-14 year age group at diagnosis and one was in the 15-19 year age group (Table 6). Among the 11 children in the Leukemia/Lymphoma subgroup, all were enrolled in the study and 8 of the children were male (73%). All leukemia diagnoses occurred before the age of 10 years with five diagnosed before the age of 5 years. All 3 children with lymphoma were diagnosed after the age of 13.

Table 6. Characteristics of 21 eligible Wilmington childhood cancer cases, 1990-2000

Characteristics	Enrolled (n=18)		Not Enrolled (n=3)	
	Number	Percent	Number	Percent
Age, years				
0-4	7	39%	--	--
5-9	4	22%	--	--
10-14	3	17%	2	67%
15-19	4	22%	1	33%
Sex				
Male	12	67%	1	33%
Female	6	33%	2	67%
Cancer Type				
Leukemia	8	44%	--	--
Lymphoma	3	17%	--	--
Bone	2	11%	1	33%
Germ Cell	1	6%	1	33%
Central Nervous System	1	6%	--	--
Hepatic	1	6%	--	--
Other Malignant Epithelial	1	6%	--	--
Renal	1	6%	--	--
Soft Tissue Sarcoma	--	--	1	33%

Nine different cancer types were represented in these children (Table 6). The most common diagnosis was leukemia (8 children: 6 with acute lymphocytic subtype or ALL and 2 with acute myeloid subtype or AML) followed by lymphoma (3 children). All children diagnosed with leukemia and lymphoma participated in the study. There were three children with bone cancer; two enrolled in the study and one did not participate. Two germ cell tumors were diagnosed (both of the intracranial and intraspinal subtype) with one child participating and one not participating in the study. The remaining five cancer types were diagnosed in one child each: central nervous system, hepatic, other malignant epithelial neoplasm (of the skin carcinoma subtype), renal, and soft tissue sarcoma. All enrolled in the study except for the child with soft tissue sarcoma.

RISK FACTOR CHARACTERISTICS OF THE STUDY POPULATION

As described in the Methods section, information on a large number of variables was collected during the interviews of cases and controls. The majority of variables were included in the interview because they were identified in the scientific literature as having a possible association with childhood cancer (e.g., exposure to ionizing radiation)

or were important for characterizing a hypothesized exposure (e.g., type of water used for drinking).

Select characteristics were included in this section and presented in Table 7. if they met any of the following criteria: 1) those with analytical results suggesting a possible association with childhood cancer in Wilmington based on having an OR >1.0 and a p-value <0.20, 2) those that are commonly reported in the literature as being major risk factors for childhood cancer even if analytical results did not suggest an association with childhood cancer among the study population, or 3) those providing basic demographic and residential information about the study population. Full detailed results of the analyses for all risk factors collected during informational interviews are contained in Appendix D.

Results are presented for all 18 participating cases and their 74 matched controls (All Cancers group) and, separately, for the 11 cases with leukemia or lymphoma and their 45 matched controls (Leukemia/Lymphoma subgroup). Table 7. provides frequencies and/or mean values comparing cases and controls for each characteristic. Odds ratios (ORs) and p-values are described in the text for select findings of interest. In addition, Table 7. provides notation to identify statistically significant associations (p <0.05) and marginally significant associations (p <0.10) between risk factors and childhood cancer in Wilmington. Readers can find all ORs and p-values in Appendix D.

Table 7. Select demographic and risk factor characteristics among cases and controls of the Wilmington Childhood Cancer Study

Characteristics	All Cancers				Leukemia/Lymphoma			
	Cases (n=18)		Controls (n=74)		Cases (n=11)		Controls (n=45)	
	#	%	#	%	#	%	#	%
Demographics								
Mean age of child, years	8.8		8.7		7.5		7.8	
Sex of child								
Male	12	67%	49	66%	8	73%	32	71%
Female	6	33%	25	34%	3	27%	13	29%
Wilmington residence								
Maternal mean, mos.	6.1		6.7		6.5		6.1	
Zero maternal	6	33%	26	35%	3	27%	17	38%
Resident at birth	12	67%	49	66%	8	73%	29	64%
Child mean, mos.	78.2		93.9		70.3		82.4	
Mother's education								
High School/GED	6	33%	17	23%	4	36%	13	29%
>High School/GED	12	67%	57	77%	7	64%	32	71%
Family cancer history[a]								
Children, <20 years	0	0%	1	<1%	0	0%	1	2%
Adults, <50 years	4	22%	14	19%	2	18%	7	16%
Prenatal Risk Factors								
Maternal age at birth[a]								
Mean age, years	28.3		29.7		28.5		29.9	
Age 35+	1	6%	8	11%	1	9%	6	13%
Pregnancy behaviors[b]								
Prenatal vitamin use	15	83%	65	88%	9	82%	41	92%
Smoking[c]	1	6%	20	27%	1	9%	11	24%
Alcohol intake	4	22%	27	37%	3	27%	15	33%
Pregnancy exposures[b]								
Diagnostic x-ray	0	0%	8	11%	0	0%	6	13%
Mononucleosis	0	0%	0	0%	0	0%	0	0%
Ultrasonography	14	78%	52	70%	9	82%	34	76%
Ionizing radiation[d]	4	22%	6	8%	3	27%	3	7%
Childhood Risk Factors								
Birth events[b]								
Given oxygen	3	17%[‡]	3	4%[‡]	2	18%[†]	3	7%[†]
Placed in incubator	5	28%	11	15%	3	27%	7	16%
Birth weight								
Low (<2500 g)	3	17%[‡]	3	4%[‡]	2	18%	2	4%
High (>4,000 g)	4	22%	14	19%	2	18%	11	24%

Characteristics	All Cancers				Leukemia/Lymphoma			
	Cases (n=18)		Controls (n=74)		Cases (n=11)		Controls (n=45)	
Adverse birth event	8	44%‡	11	15%‡	5	46%‡	7	16%‡
Other medical history								
Breastfed[b]	9	50%	40	54%	5	46%	24	53%
Mononucleosis	2	11%	4	5%	1	9%	3	7%
Antihistamine use	10	56%†	25	34%†	5	46%	14	31%
Exposures[e]								
Second-hand smoke	4	22%†	36	49%†	1	9%	21	47%
Bug repellent or pesticides	13	72%	58	78%	9	82%	32	71%
Household Exposures[f]								
Metals, alloys, solders	5	28%	10	14%	5	46%	4	9%
Plastics, synthetics, resins	7	39%	17	23%	5	46%†	8	18%†
Exhaust fumes	3	17%	6	8%	2	18%	2	4%
Herbicides	12	67%	40	54%	8	73%	21	47%

[a]Excludes one control mother whose child was adopted
[b]Includes responses from biological mothers only
[c]During year before birth
[d]During two years before birth through diagnosis/reference date
[e]Child exposed at home or during activities from birth through diagnosis/reference date
[f]Products used by child or anyone living with the child, or applied in or around the home at any time from one month before pregnancy through diagnosis/reference date
†Marginally significant association with the odds of childhood cancer ($p < 0.10$)
‡Statistically significant association with the odds of childhood cancer ($p < 0.05$)

Demographics

Demographic characteristics of cases and controls are summarized in Table 7. . Because controls were matched to cases based on age and sex, the distribution of these variables for controls was nearly identical to those of the cases in both cancer groups. Controls were found to have spent about 20% more time as residents of Wilmington as children— 93.9 months (standard deviation = 67.5), on average, versus 78.2 months for cases (standard deviation = 60.6). A similarly sized difference was observed among the Leukemia/Lymphoma subgroup. These differences were not statistically significant for either group. The minimum and maximum time of residence was approximately 1.5 years and 15.5 years for all cases and for the Leukemia/Lymphoma subgroup. For all controls, it was 6 months and 19 years and, for the Leukemia/Lymphoma subgroup controls, the minimum was 6 months and the maximum was 15.5 years.

The average maternal residence in Wilmington during the year before birth for cases was 6.1 months (standard deviation = 5.8) and for controls was 6.7 months (standard

deviation = 5.7). About one third of mothers, both cases and controls, did not reside in Wilmington until after their child was born. Approximately two-thirds of both cases and controls were born as residents of Wilmington. Similar residential history was observed among the Leukemia/Lymphoma subgroup. All study mothers completed at least high school or received a General Equivalency Diploma (GED). Similar educational achievement was reported for mothers of cases and controls, although a slightly higher percentage of case mothers completed only high school or a GED.

Information on the health history of blood relatives was obtained with specific interest in cancer, chromosomal abnormalities, and hereditary conditions. Only one participant reported a blood relative (defined as a child's sibling, half-sibling, parent, or grandparent) with a history of childhood cancer, a control's father who was diagnosed at the age of 19. Cancer in adult blood relatives before the age of 50 was reported by four cases (22%) and fourteen controls (19%); the Leukemia/Lymphoma subgroup reported similar proportions. Among those, three controls reported multiple blood relatives with cancer prior to age 50, one of whom is part of the Leukemia/Lymphoma subgroup. No cases reported multiple cancers in relatives prior to the age of 50.

Prenatal Risk Factors

Table 7. presents a summary of the major maternal pregnancy behaviors and exposure characteristics obtained during informational interviews for cases and controls in both the All Cancers and Leukemia/Lymphoma groups.

A detailed reproductive medical history was sought for each of the biological mothers (n=16 for cases and n=70 for controls). For six children (2 cases and 4 controls), the biological mother was not available for interview. This resulted in some missing maternal medical history during pregnancy and some missing maternal behavioral and exposure characteristics for those six children. Unless noted as pertaining to biological mothers only, the data presented refers to all mothers.

Maternal Age at Birth
Maternal age at birth was similar between cases and controls. The proportion of mothers who were 35 or older at the time of their child's birth was somewhat higher among control mothers (11%) compared with case mothers (6%). This difference was not statistically significant (p = 0.52). Results for maternal age were similar for the Leukemia/Lymphoma subgroup.

Pregnancy Behaviors
Information on mothers' behaviors during pregnancy was obtained when the biological mothers were available for interview. Smoking exposure was defined as 'yes' if a mother

smoked every day for 3 months or longer during the year before the child's birth. In the All Cancers group, only one case mother (6%) reported smoking during this period compared to 20 control mothers (27%). Findings were similar in the Leukemia/Lymphoma subgroup (9% vs. 24%). These findings were not statistically significant (All Cancers p = 0.17; Leukemia/Lymphoma p = 0.33). Similarly, alcohol consumption during pregnancy was somewhat less common among case mothers compared to control mothers in the All Cancers group (22% vs. 37%), though the finding was not statistically significant. Within the Leukemia/Lymphoma subgroup, a similar proportion of case and control mothers consumed alcohol during pregnancy (27% vs. 33%). Finally, prenatal vitamin use during pregnancy was fairly similar between cases and controls in the All Cancers group (83% vs. 88%), but was somewhat lower among cases compared to controls within the Leukemia/Lymphoma subgroup (82% vs. 92%). This difference was not statistically significant.

Pregnancy Exposures
Mothers were also asked about any potential occupational exposure to ionizing radiation while they were pregnant. Overall, mothers of cases in both cancer groups were more often occupationally exposed to ionizing radiation while pregnant compared to mothers of controls (All Cancers 22% vs. 8%; Leukemia/Lymphoma 27% vs. 7%), but these differences are not statistically significant (All Cancers p = 0.14; Leukemia/Lymphoma p = 0.102). Among those who reported occupational ionizing radiation exposure, only one case mother and two control mothers reported having worked within 20 feet of an active ionizing radiation source for any length of time during pregnancy. In all three instances, the women worked near an x-ray device in a healthcare setting.

Diagnostic x-ray exposure was reported during pregnancy by eight (11%) control mothers (6 of whom are in the Leukemia/Lymphoma subgroup) but no case mothers. Among the All Cancers group, there was a somewhat higher proportion of case mothers (78%) who had any prenatal ultrasound examinations compared to control mothers (70%), though these results were not statistically significant (p = 0.11). The comparison between case and control mothers was similar among the Leukemia/Lymphoma subgroup (82% vs. 76%), however statistical significance could not be calculated for this comparison because there were no discordant pairs.

No mothers reported having mononucleosis during pregnancy.

Childhood Risk Factors

This section describes major findings observed for risk factors experienced during childhood including adverse birth events, other childhood medical history, and

childhood exposures. Detailed results of all analyses of childhood medical events at birth, medical history, and environmental exposures can be found in Appendix D.

<u>Birth events</u>
There were proportionally more cases born with low birth weight (17%) compared to controls (4%) within the All Cancers group, and this difference was statistically significant (p = 0.03). The corresponding odds ratio was substantially elevated, but the confidence interval was very wide, indicating imprecision in the estimate due to small numbers (OR = 13, 95% CI: 1.3-123). The OR for the Leukemia/Lymphoma subgroup could not be calculated because all cases and their matched controls gave the same response to this question (i.e., there were no discordant pairs). The proportion of high birth weight case and control children was similar within both the All Cancers group (22% vs. 19%) and the Leukemia/Lymphoma subgroup (18% vs. 24%).

A similarly statistically significant result in the All Cancers group was found for children immediately given oxygen after birth (OR = 14; 95% CI: 1.4-130). Again, the confidence interval was very wide due to the small numbers of cases (n=3) and controls (n=3). The estimated OR for the Leukemia/Lymphoma subgroup was also elevated but was only marginally significant with a p-value of 0.08 (OR = 8.6; 95%CI: 0.8-96) and the number of cases and controls affected was small (cases = 2; controls = 3).

Case children were also found to be more often placed in an incubator immediately after birth (All Cancers: 28% of cases vs. 15% of controls; Leukemia/Lymphoma: 27% of cases vs. 16% of controls. The odds of cancer following this event were elevated but were not statistically significant (All Cancers OR = 2.8, 95%CI 0.8-10; Leukemia/Lymphoma OR = 4.3, 95%CI: 0.7-27).

Since there was overlap among children who were reported to have received oxygen at birth, been placed in an incubator immediately following birth, or been born with low birth weight, a composite variable named "adverse birth event" was created to assess these events together as one risk factor. When evaluated collectively as a single risk factor, more cases than controls had a history of any of these three "adverse birth events," and the differences in both cancer groups was statistically significant. These children were more likely to be diagnosed with cancer (All Cancers OR = 6.0, 95% CI: 1.7-21; Leukemia/Lymphoma OR = 16; 95% CI: 1.8-140). As with the three birth risk factors evaluated individually, the wide confidence intervals indicate that the ORs are very imprecise, particularly for the Leukemia/Lymphoma subgroup.

<u>Other Childhood Medical History</u>
The proportion of breastfed case and control children was fairly similar within both the All Cancers group (50% vs. 54%) and the Leukemia/Lymphoma subgroup (46% vs. 53%). A higher proportion of cases had a history of mononucleosis compared to controls (11% vs. 5%), but the difference was not statistically significant. There were no reported instances of autoimmune disorders, HIV infection, cytomegalovirus infection, organ transplant, hypogammaglobinemia, or use of antiepileptic drugs or chemotherapy drugs among cases or controls.

The only medicinal exposure that appeared to be potentially associated with cancer diagnosis was antihistamine use. Antihistamine use was reported more frequently among cases (56%) than controls (34%). The resulting OR for all cancers combined was elevated but was only marginally significant (OR 2.7; 95% CI 0.8-8.7; p = 0.0954). The Leukemia/Lymphoma subgroup resulted in a non-significant OR of 1.9 (95% CI 0.5-7.9, p = 0.37).

<u>Childhood Exposures</u>
Similar to the findings for smoking during pregnancy, more control children were reported to have been exposed to second-hand smoke than were case children (All Cancers: 22% of cases vs. 49% of controls; Leukemia/Lymphoma: 9% of cases vs. 47% of controls). The odds ratio for this association in the All Cancers analysis (OR: 0.3; 95% CI 0.1-1.02) was marginally statistically significant with a p-value of 0.053, but the OR for the Leukemia/Lymphoma subgroup could not be calculated (Appendix D).

Exposure to bug repellants or pesticides was somewhat similar among cases and controls in the All Cancers group (72% vs. 78%). In the Leukemia/Lymphoma subgroup, there was a slightly larger difference between cases and controls in the use of these products (82% vs. 71%). The small differences in both groups were not statistically significant.

Household Exposures

It was not always possible to separate household exposures between the prenatal or post birth periods because of the nature of the question asked or the response provided. For example, exposure by a child to various chemicals was determined by asking if anyone living in the house worked with the chemical in or around the home at any time from one month prior to conception to the child's diagnosis/reference date or if the child her/himself used the chemical. For the household exposure variables presented in Table 7. , most mothers who reported prenatal exposure also reported child exposures after birth. However, some exposures may have occurred only after birth and interview data did not always enable differentiation of the exposure period.

Plastics, synthetics, or resins

Potential exposure to plastics, synthetics, or resins was found to be more common among cases than among controls (All Cancers: 39% vs. 23%; Leukemia/Lymphoma: 46% vs. 18%) and resulted in elevated ORs for both the All Cancers and Leukemia/Lymphoma groups. The OR for the association between this exposure and All Cancers was 2.3 (95% CI 0.71-7.4) and not statistically significant, but a marginally significant OR of 4.2 (95% CI 0.96-18) was observed for Leukemia/Lymphoma (p = 0.06).

Metals, alloys, solders

For use of metals, alloys, or solders in and around the household, an elevated but non-statistically significant OR of 2.8 (95% CI 0.7-10) was found in the All Cancers group (the OR could not be calculated for the Leukemia/Lymphoma subgroup – see Appendix D). In almost all instances, the father of the case or control child was the individual using these materials.

Exhaust fumes

A slightly higher proportion of case respondents reported exposure to exhaust fumes compared to controls within both the All Cancers group and Leukemia/Lymphoma sub group (17% vs. 8% and 18% vs. 4%, respectively). The corresponding ORs were elevated, but neither difference was statistically significant (All Cancers OR = 2.0, 95% CI 0.5-8.9; LL OR = 3.9, 95% CI 0.6-28).

Herbicides

Similarly, there were non-statistically significant associations between herbicide exposure and case/control status (All Cancers: 67% of cases versus 54% of controls; Leukemia/Lymphoma: 73% of cases versus 47% of controls). The p-value for the All Cancers analysis was 0.40, and for the Leukemia/Lymphoma analysis the p-value was 0.12 (OR = 3.6; 95% CI: 0.7-18).

DRINKING WATER CONTAMINANTS

N-Nitrosodimethylamine (NDMA)

Summary of Modeled Average NDMA Concentrations
Figure 10. A and Figure 11 show the distribution of the average modeled monthly NDMA concentration for the entire study population for the maternal and childhood exposure periods, respectively. Fifty-eight (63%) of the mothers in the study are estimated to have had no NDMA in their residential drinking water during the year before their child was born, and 16 (17%) of the children are estimated to have had no childhood residence with NDMA contaminated drinking water. The remaining non-zero concentration

estimates are roughly normally distributed with a few high and low values and more frequent values in the middle of the range.

Figure 10. Average modeled monthly NDMA concentrations (ng/L) in drinking water during the 12 months before birth for mothers in the Wilmington Childhood Cancer Study (n=92)
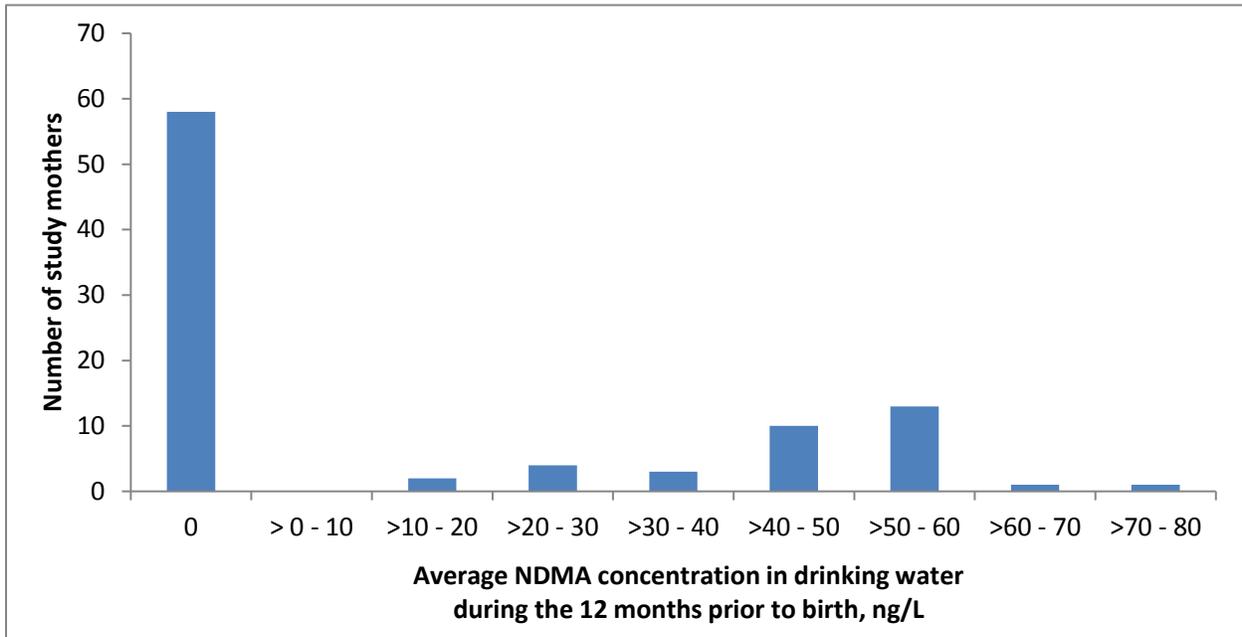
NOTE: Except where all monthly NDMA concentration estimates were zero, averages include non-zero values only.

Figure 11. Average modeled monthly NDMA concentrations (ng/L) in drinking water for children in the Wilmington Childhood Cancer Study (n=92)
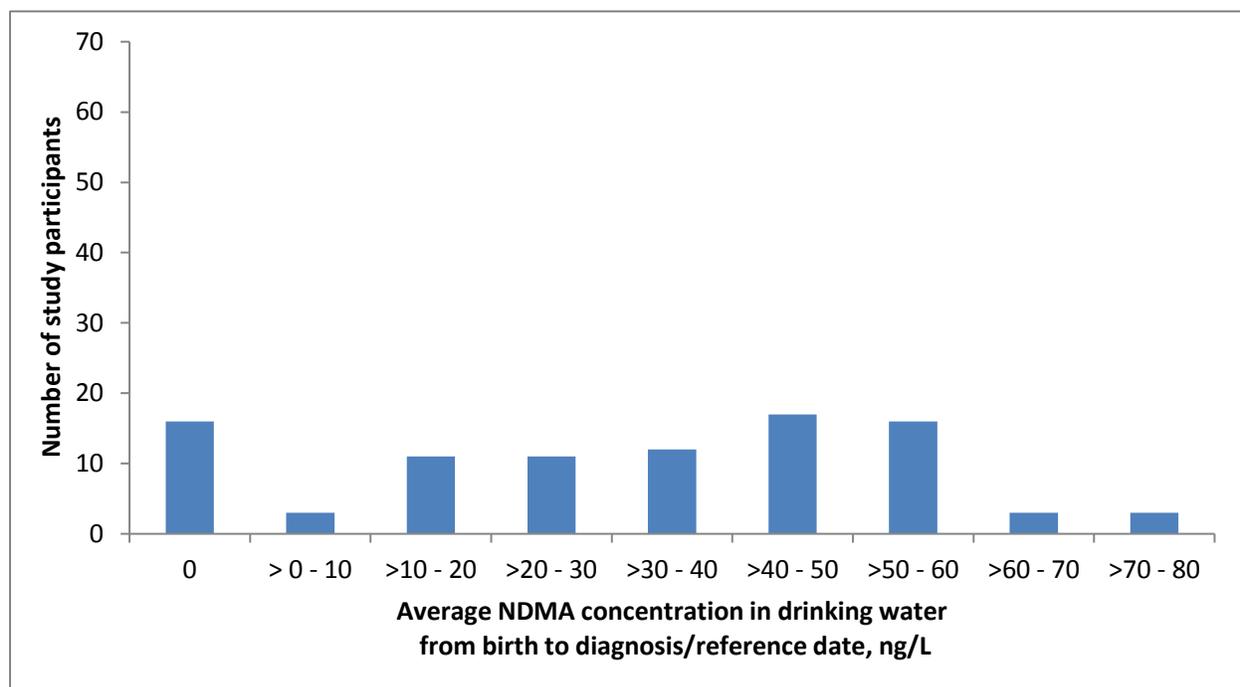
NOTE: Except where all monthly NDMA concentration estimates were zero, averages include non-zero values only.

NDMA Concentrations: Cases versus Controls

Table 8 summarizes the estimated residential NDMA concentrations separately for cases and controls for the maternal and childhood exposure periods. During the maternal exposure period, mothers of cases were more likely to have had any NDMA in their residential tap water and had greater estimated concentrations of NDMA compared to mothers of controls. Specifically, 50% of case mothers were estimated to have had NDMA present in their tap water during at least one month in the year prior to the child's birth compared to 34% of control mothers, and the median non-zero monthly concentration estimated at the tap of case mothers was 52 ng/L compared to 47 ng/L for control mothers. Similar results are seen in the Leukemia/Lymphoma subgroup. Estimated median non-zero concentrations during the childhood period were also higher for cases compared to controls (51 ng/L versus 39 ng/L). However, the likelihood of having had any NDMA in residential tap water during childhood was similar for cases and controls (78% vs. 84%). Similar results are seen in the Leukemia/Lymphoma subgroup. In all comparisons, controls had a somewhat lower minimum non-zero monthly NDMA concentration and a slightly higher maximum monthly NDMA concentration compared to cases.

Table 8. Estimated residential NDMA concentrations among the Wilmington study population for maternal[a] and childhood[b] exposure periods

Study Group	Participants with Any Non-Zero Value (%)	Estimated NDMA Concentration (ng/L)		
		Median Non-Zero Monthly Value	Minimum Non-Zero Monthly Value	Maximum Monthly Value
All Cancers				
Maternal				
Cases (n=18)	50%	52	25	62
Controls (n=74)	34%	47	12	73
Childhood				
Cases (n=18)	78%	51	11	67
Controls (n=74)	84%	39	6.8	76
Leukemia/Lymphoma				
Maternal				
Cases (n=11)	64%	53	25	62
Controls (n=45)	36%	45	19	73
Childhood				
Cases (n=11)	73%	55	28	67
Controls (n=45)	84%	42	6.9	70

[a]Maternal period includes the 12 months prior to child's birth.
[b]Childhood period extends from birth to diagnosis/reference date.

NDMA in Drinking Water and Childhood Cancer

Dichotomous (ever/never) exposure potential

Table 9. presents results of conditional logistic regression models evaluating the association between development of childhood cancer and dichotomous (ever/never) presence of NDMA in drinking water. When evaluating maternal exposure, the odds of childhood cancer (all cancers and leukemia/lymphoma only) were higher for children whose mothers ever lived in a home estimated to have NDMA contaminated drinking water during the year prior to birth, but these results did not reach statistical significance. There was no elevation in the odds of childhood cancer for those who lived in homes estimated to have had NDMA contamination as children compared to those who did not (OR = 0.7; 95% CI: 0.2-2.5). When restricting the analysis to leukemia or lymphoma only, the odds were even lower among children ever to have NDMA present in their home drinking water (OR = 0.5) and the result was not statistically significant (*p* = 0.38).

Table 9. Presence of NDMA in drinking water and odds of childhood cancer among children living in Wilmington, MA, 1974-2000

All Cancers	Cases (n=18)		Controls (n=74)		ORᵃ	95% CIᵇ	p-value
	n	(%)	n	(%)			
Maternal, Ever NDMA	9	(50)	25	(34)	2.2	(0.7, 7.0)	0.18
Childhood, Ever NDMA	14	(78)	62	(84)	0.7	(0.2, 2.5)	0.55
Leukemia/Lymphoma	Cases (n=11)		Controls (n=45)		ORᵃ	95% CIᵇ	p-value
	n	(%)	n	(%)			
Maternal, Ever NDMA	7	(64)	16	(36)	2.9	(0.8, 11)	0.12
Childhood, Ever NDMA	8	(73)	38	(84)	0.5	(0.1, 2.5)	0.38

[a]OR = Matched Odds Ratio
[b]95% CI = 95% Confidence Interval

Categorical (zero/low/high) exposure potential

Average NDMA concentrations were also categorized into three groups as described in the methods section of this report. Table 10 and Figure 12. O present the results of conditional logistic regression models evaluating the association between development of childhood cancer (all cancers and leukemia/lymphoma only) and zero, low, or high average NDMA concentrations in drinking water. For the association between maternal residential NDMA concentrations in drinking water and the development of childhood cancer, a positive trend was observed for higher odds of any cancer (ORs = 1.0, 1.3, 3.0) and of leukemia/lymphoma alone (ORs = 1.0, 1.3, 5.0) for increasing average NDMA concentrations in drinking water from zero to low to high. The odds ratio of 5.0 for the high concentration group in the leukemia/lymphoma sub-analysis was statistically significant, although the confidence interval is very wide. This indicates that there was a statistically significant elevation in the odds of childhood leukemia or lymphoma for those with the highest average estimated concentrations in maternal residential drinking water. However, the actual effect estimate of 5.0 is imprecise. The OR for the high category of the All Cancers analysis was of marginal statistical significance ($p = 0.09$). A test of trend for the All Cancers combined analysis resulted in a p-value of 0.12; for the leukemia/lymphoma analysis, the trend test resulted in a p-value of 0.06.

In contrast to the results for maternal NDMA concentrations in drinking water, when evaluating concentrations estimated to have been present in residential drinking water during childhood, there was no evidence of a positive association between NDMA in drinking water with development of childhood cancer in general (OR = 0.9 for the high concentration category) or with development of leukemia or lymphoma (OR = 0.6 for the high concentration category).

Table 10. Average estimated concentration of NDMA in drinking water* (zero, low, high) and odds of childhood cancer among children living in Wilmington, MA, 1974-2000

All Cancers	Cases (n=18)		Controls (n=74)		OR[a]	95% CI[b]	*p*-value	Trend Analysis *p*-value
	n	(%)	n	(%)				
Maternal								
Zero	9	(50%)	49	(66%)	1.0	-ref-		
Low	3	(17%)	14	(19%)	1.3	(0.3, 6.2)	0.75	
High	6	(33%)	11	(15%)	3.0[†]	(0.8, 11)	0.09	0.12
Childhood								
Zero	4	(22%)	12	(16%)	1.0	-ref-		
Low	5	(28%)	33	(45%)	0.4	(0.1, 2.0)	0.27	
High	9	(50%)	29	(39%)	0.9	(0.2, 3.5)	0.86	0.78
Leukemia/ Lymphoma	Cases (n=11)		Controls (n=45)		OR[a]	95% CI[b]	*p*-value	Trend Analysis *p*-value
	n	(%)	n	(%)				
Maternal								
Zero	4	(36%)	29	(64%)	1.0	-ref-		
Low	2	(18%)	10	(22%)	1.3	(0.2, 8.7)	0.77	
High	5	(45%)	6	(13%)	5.0[‡]	(1.0, 24)	0.046	0.06
Childhood								
Zero	3	(27%)	7	(16%)	1.0	-ref-		
Low	3	(27%)	20	(44%)	0.3	(0.04, 2.3)	0.26	
High	5	(45%)	18	(40%)	0.6	(0.1, 3.3)	0.54	0.79

[a]OR = Matched Odds Ratio
[b]95% CI = 95% Confidence Interval
†Marginally significant association with the odds of childhood cancer (*p* <0.10)
‡Statistically significant association with the odds of childhood cancer (*p* <0.05)
*NOTES: Average concentrations include months of non-zero estimates only. For the All Cancers analysis, average maternal concentrations ranged from 12 to 47 ng/L in the low category and 48 to 73 ng/L in the high category; average childhood concentrations ranged from 6.8 to 40 ng/L in the low category and 40 to 76 ng/L in the high category. For the Leukemia/Lymphoma analysis, average maternal concentrations ranged from 19 to 47 ng/L in the low category and 50 to 73 ng/L in the high category; average childhood concentrations ranged from 6.9 to 43 ng/L in the low category and 43 to 70 ng/L in the high category.

Figure 12. Odds ratios and 95% confidence intervals for the association between childhood cancer and average estimated NDMA concentrations in drinking water during maternal (the year before birth) and childhood exposure periods
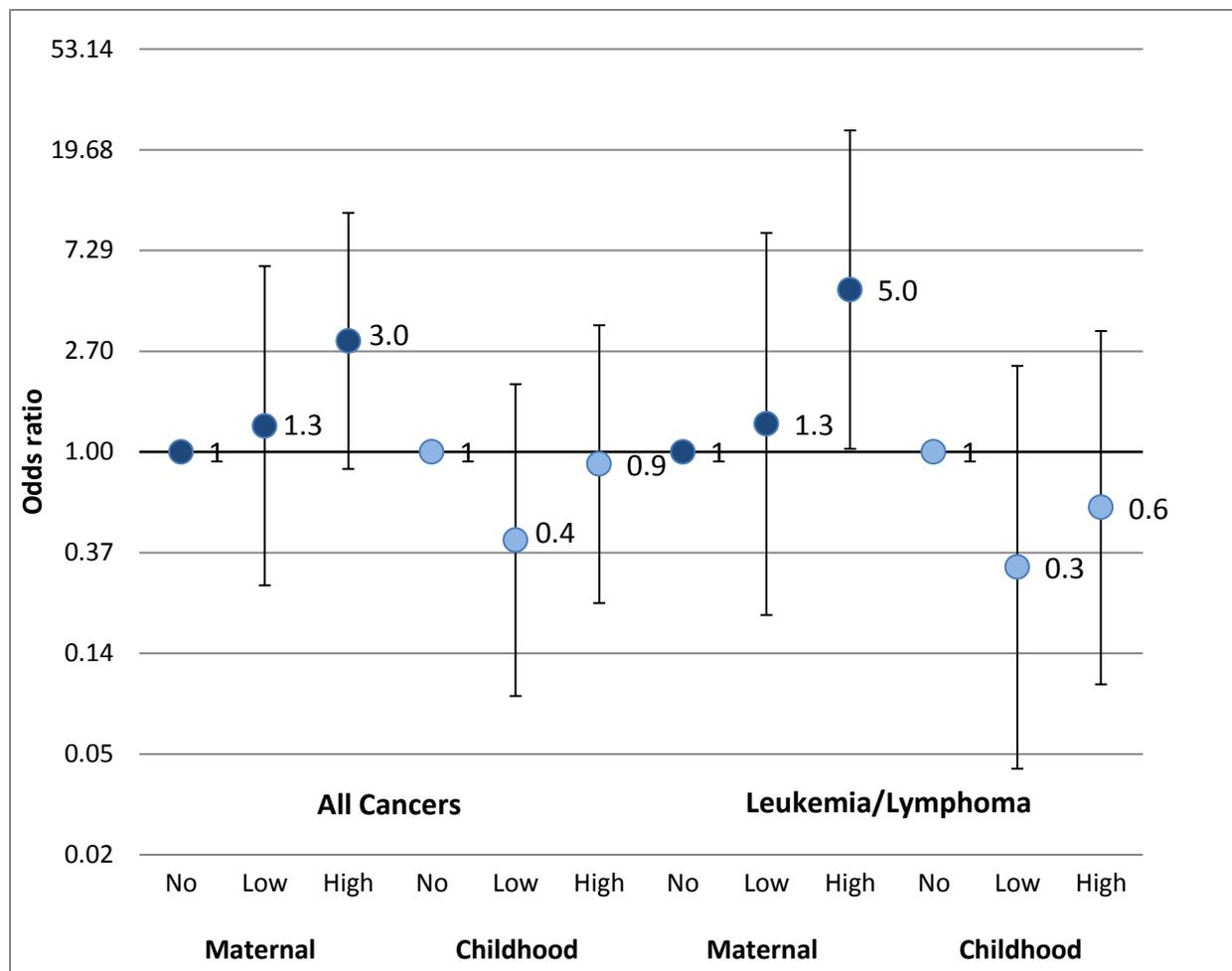
Duration of Exposure

In addition to average NDMA concentration, duration of potential exposure was also evaluated for its association with the probability of childhood cancer development. The number of months with a non-zero estimated NDMA concentration in drinking water was evaluated for the maternal and childhood periods separately. In addition, the total number of months of residence in the town of Wilmington was evaluated for both the maternal and childhood periods. Only total time of residence during childhood was significantly associated with childhood cancer and the association was negative. In other words, the odds of childhood cancer were lower with increasing months of residence (OR = 0.98; 95% CI: 0.95-0.997). For the Leukemia/Lymphoma subgroup, there were

no significant associations between duration of potential exposure and development of cancer.

When duration variables were included in logistic regression models evaluating average NDMA concentration as a predictor of childhood cancer, the associated odds ratios were only modestly affected. There continued to be a positive association between maternal period NDMA concentrations and development of childhood cancer (all cancers and leukemia/lymphoma), slightly attenuated after adjusting for duration as non-zero months of potential exposure and slightly strengthened after adjusting for duration as total Wilmington residence. Childhood period NDMA concentrations continued to show no positive associations with childhood cancer.

Trichloroethylene (TCE)

<u>Summary of Modeled Average TCE Concentrations</u>
Figure 13 and Figure 14 show the distribution of the average modeled monthly TCE concentration for the subset of the study population for whom TCE could be estimated for maternal exposure (n=73) and for childhood exposure (n=58), respectively. Fifty–four (74%) of the mothers are estimated to have had no TCE in their residential drinking water during the year before their child was born, and 28 (48%) of the children are estimated to have had no childhood residence with TCE contaminated drinking water. The remaining non-zero concentration estimates skew towards the lower end of the range with only a small numbers of study participants having higher concentrations.

Figure 13. Average modeled monthly TCE concentrations (μg/L) in drinking water during the 12 months before birth for mothers in the Wilmington Childhood Cancer study (n=73)
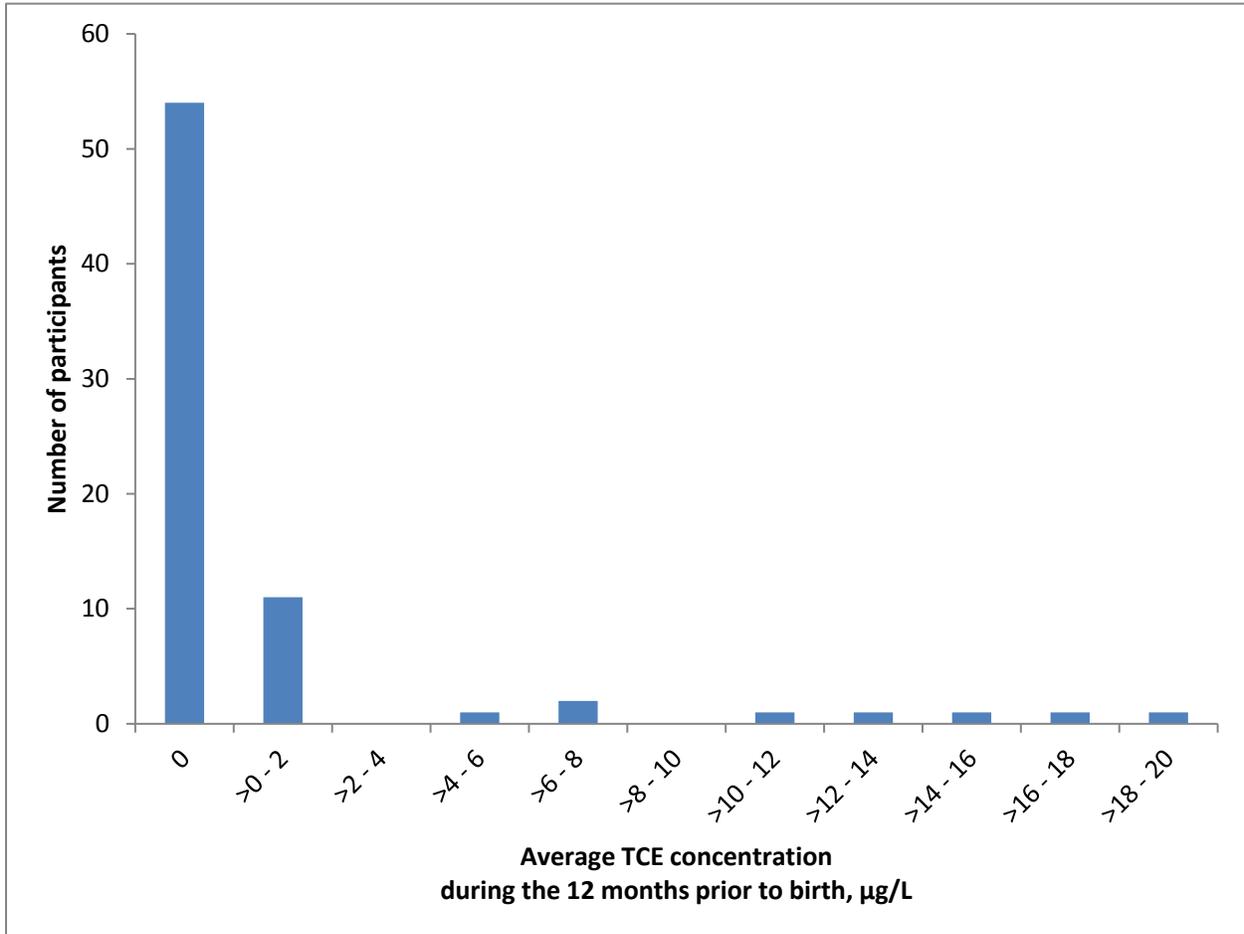
NOTE: Except where all monthly TCE concentration estimates were zero, averages include non-zero values only.

Figure 14. Average modeled monthly TCE concentrations (µg/L) in drinking water for children in the Wilmington Childhood Cancer Study (n=58)
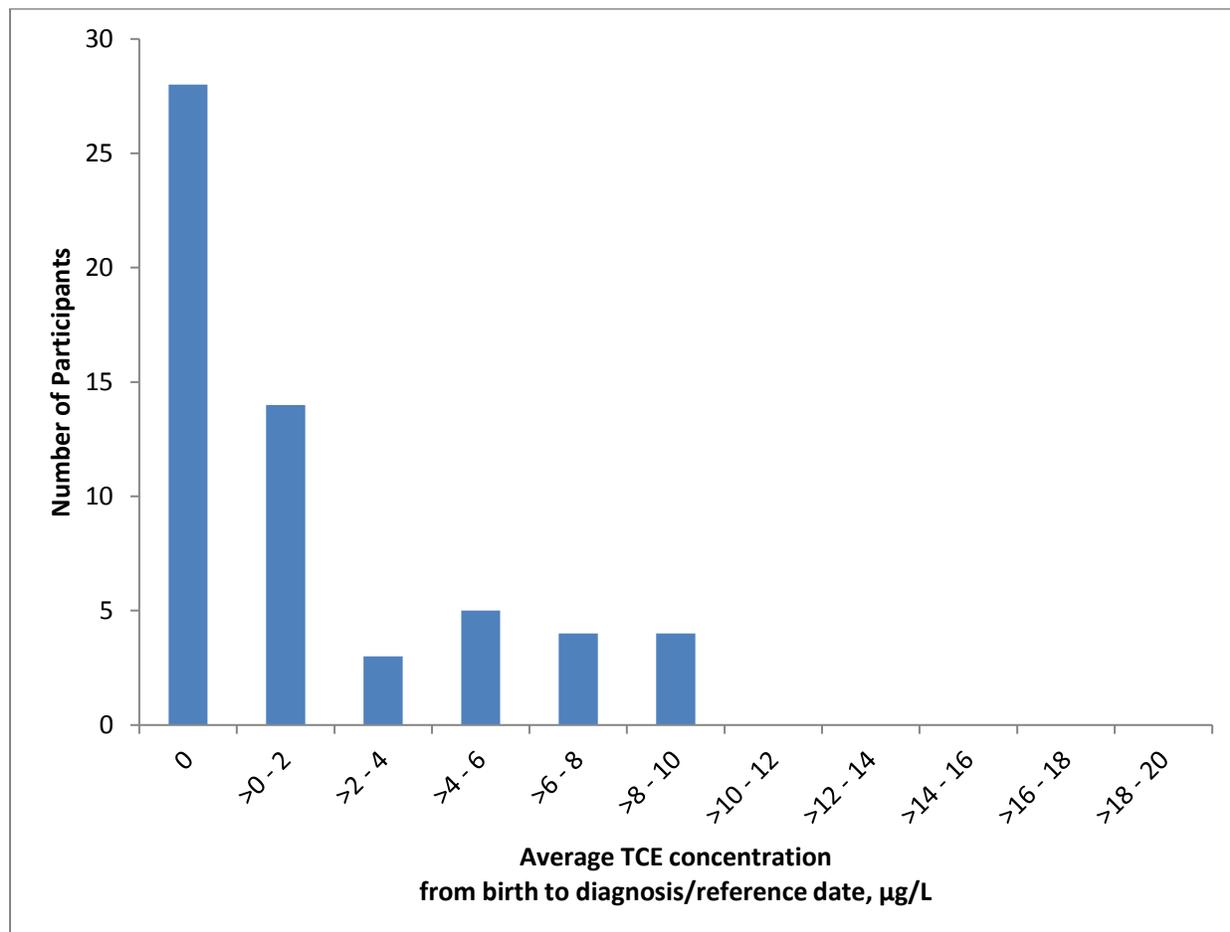
NOTE: Except where all monthly TCE concentration estimates were zero, averages include non-zero values only.

TCE Concentrations: Cases and Controls

Table 11. summarizes the estimated residential TCE concentrations separately for cases and controls for the maternal and childhood exposure periods. During the maternal exposure period, mothers of cases were slightly more likely to have had any TCE in their residential tap water compared to mothers of controls (31% compared to 25%), but median concentrations were similar between the two groups. Similar results are seen in the Leukemia/Lymphoma subgroup. The inverse is true for the childhood exposure period with controls being slightly more likely to have had at least one month with TCE estimated to be present in their tap water (53% of controls compared to 46% of cases). However, estimated median non-zero concentrations during the childhood period were approximately twice as high for cases compared to controls (5.2 µg/L versus 2.1 µg/L). Similar results are seen in the Leukemia/Lymphoma subgroup.

Table 11. Estimated residential TCE concentrations among the Wilmington study population for maternal[a] and childhood[b] exposure periods

| Study Group | Participants with Any Non-Zero Value (%) | Estimated TCE Concentration (µg/L) | | |
		Median Non-Zero Monthly Value	Minimum Non-Zero Monthly Value	Maximum Monthly Value
All Cancers				
Maternal				
Cases (n=16)	31%	1.0	0.08	19
Controls (n=57)	25%	0.8	0.06	18
Childhood				
Cases (n= 13)	46%	5.2	0.09	6.7
Controls (n=45)	53%	2.1	0.05	9.2
Leukemia/Lymphoma				
Maternal				
Cases (n=10)	30%	6.4	1.0	19
Controls (n=39)	23%	6.4	0.1	18
Childhood				
Cases (n=8)	38%	6.1	5.3	6.7
Controls (n=28)	54%	3.2	0.1	9.2

[a]Maternal period includes the 12 months prior to child's birth.
[b]Childhood period extends from birth to diagnosis/reference date.

Correlation between NDMA and TCE

Due to overlapping time periods of potential exposure, the exposure to both NDMA and TCE was possible for some study participants. Focusing on the maternal exposure period, Table 12 and Figure 15 provide information on the association between these two contaminants among the subset of the study population for whom concentrations of both NDMA and TCE could be estimated. As shown in Table 12, a slightly higher percentage of case mothers are estimated to have experienced exposure to both contaminants during the year before their child's birth (31% of cases vs. 25% of controls). Among cases, 50% are estimated to have been unexposed to either contaminant and, among controls, the doubly unexposed proportion is estimated at 58%. The remaining mothers are believed to have been exposed to NDMA, but not to TCE.

Table 12. Presence of NDMA and TCE in maternal residential drinking water among cases and controls of the Wilmington Childhood Cancer Study (n=73)

Cases (n=16)	Controls (n=57)

	NDMA	
	Yes	No
TCE Yes	5 (31%)	0 (0%)
TCE No	3 (19%)	8 (50%)

	NDMA	
	Yes	No
TCE Yes	14 (25%)	0 (0%)
TCE No	10 (18%)	33 (58%)

Besides the large number of study participants that were unexposed to either contaminant, there is not a strong correlation with respect to estimated average concentrations of NDMA and TCE (Figure 15). The Pearson correlation coefficient (r) for the relationship is 0.35 with a significant p-value of 0.002, resulting in an R^2 value of 0.13. This means that there is a statistically significant correlation, but that the overall relationship is not strong with only 13% of the variation in NDMA concentrations explained by corresponding TCE concentrations. The correlation is driven by the large number of participants with estimated zero exposure to both compounds; when the doubly unexposed are excluded, no correlation is observed (r=0.005; p = 0.98).

Figure 15. Scatterplot of average maternal NDMA and TCE concentrations among participants of the Wilmington Childhood Cancer Study, n=73
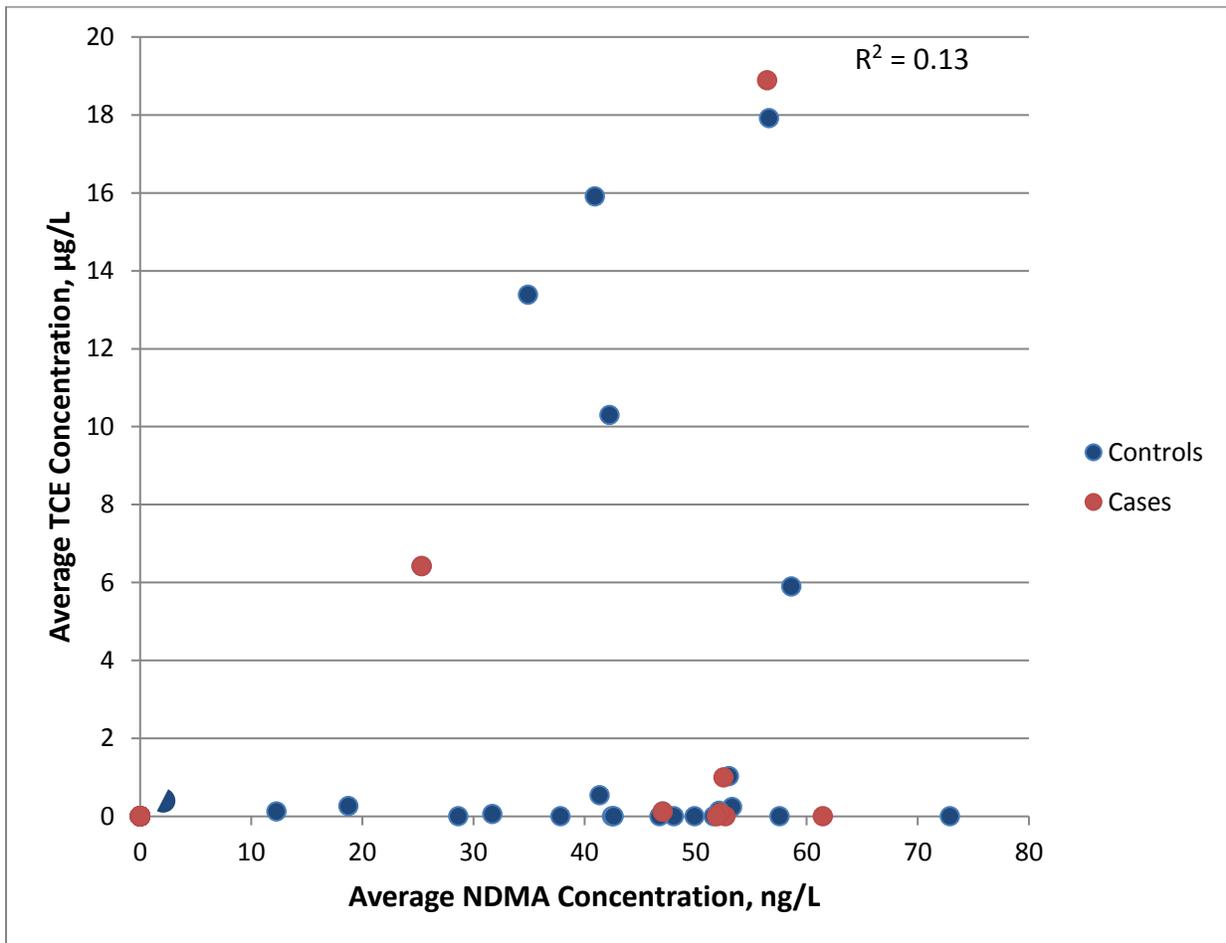
Note: Points may represent more than one individual [e.g., the "0,0" point represents all 41 participants (8 cases, 33 controls) with no exposure to either NDMA or TCE].

TCE in Drinking Water and Childhood Cancer

Dichotomous (ever/never) exposure potential

Table 13. presents results of conditional logistic regression models evaluating the association between development of childhood cancer and dichotomous (ever/never) presence of TCE in drinking water. When evaluating maternal exposure, odds of childhood cancer (all cancers and leukemia/lymphoma only) were higher for children whose mothers ever lived in a home estimated to have TCE-contaminated drinking water during the year prior to birth, but these results do not reach statistical significance and the confidence intervals are very wide. There was no elevation in the odds of childhood cancer for those who lived in homes estimated to have had TCE contamination as children compared to those who did not (OR = 0.2; 95% CI: 0.02-2.1).

When restricting the analysis to leukemia or lymphoma only, the association with childhood presence of TCE in drinking water was incalculable due to few discordant pairs.

Table 13. Presence of TCE in drinking water and odds of childhood cancer among children living in Wilmington, MA, 1981-2000

All Cancers	Cases (n=16)		Controls (n=57)		OR[a]	95% CI[b]	p-value
	n	(%)	n	(%)			
Maternal, Ever TCE	5	(31%)	14	(25%)	2.3	(0.5, 12)	0.32
	Cases (n=13)		Controls (n=45)				
Childhood, Ever TCE	6	(46%)	24	(53%)	0.2	(0.02, 2.1)	0.18
Leukemia/Lymphoma	Cases (n=10)		Controls (n=39)				
Maternal, Ever TCE	3	(30%)	9	(23%)	1.7	(0.3, 11)	0.55
	Cases (n=8)		Controls (n=28)				
Childhood, Ever TCE	3	(38%)	15	(54%)	NC	NC	NC

[a]OR = Matched Odds Ratio
[b]95% CI = 95% Confidence Interval
NC = Not calculable due to insufficient data (i.e. few discordant pairs)

Categorical (zero/low/high) exposure potential

Average TCE concentrations were also categorized into three groups as described in the methods section of this report.

Table 14. presents the results of conditional logistic regression models evaluating the association between development of childhood cancer and zero, low, or high average TCE concentrations in drinking water. As shown in

Table 14. , results for childhood exposure models restricted to the Leukemia/Lymphoma subgroup could not be calculated due to having too few discordant pairs for analysis. There was an elevated probability for the development of any childhood cancer associated with the low TCE concentration category during the maternal exposure period (OR = 4.2; 95% CI: 0.3-51), but the result was not statistically significant, confidence intervals were very wide, and there was no consistent dose response effect (trend test *p*-value = 0.80). A similar result was observed in the Leukemia/Lymphoma subgroup analysis. When evaluating childhood TCE concentration estimates, there was no evidence of a positive association with development of childhood cancer.

Table 14. Average estimated concentration of TCE in drinking water* (zero, low, high) and odds of childhood cancer among children living in Wilmington, MA, 1981-2000

All Cancers Maternal	Cases (n=16)		Controls (n=57)		OR[a]	95% CI[b]	p-value	Trend Analysis p-value
	n	(%)	n	(%)				
Zero	11	(69%)	43	(75%)	1.0	-ref-		
Low	3	(19%)	7	(12%)	4.2	(0.3, 51)	0.26	
High	2	(13%)	7	(12%)	1.3	(0.1, 13)	0.81	0.80
Childhood	Cases (n=13)		Controls (n=45)					
	n	(%)	n	(%)				
Zero	7	(54%)	21	(47%)	1.0	-ref-		
Low	2	(15%)	13	(29%)	0.2	(0.02, 2.1)	0.17	
High	4	(31%)	11	(24%)	0.2	(0.01, 4.6)	0.33	0.96
Leukemia/ Lymphoma Maternal	Cases (n=10)		Controls (n=39)		OR[a]	95% CI[b]	p-value	Trend Analysis p-value
	n	(%)	n	(%)				
Zero	7	(70%)	30	(77%)	1.0	-ref-		
Low	2	(20%)	5	(13%)	1.9	(0.3, 12)	0.51	
High	1	(10%)	4	(10%)	1.2	(0.03, 49)	0.92	0.94
Childhood	Cases (n=8)		Controls (n=28)					
	n	(%)	n	(%)				
Zero	5	(63%)	13	(46%)	1.0	-ref-		
Low	0	(0%)	9	(32%)	NC	NC	NC	
High	3	(38%)	6	(21%)	NC	NC	NC	0.27

[a]OR = Matched Odds Ratio
[b]95% CI = 95% Confidence Interval
NC = Not calculable due to insufficient data (i.e. few discordant pairs)
*NOTES: Average concentrations include months of non-zero estimates only. For the All Cancers analysis, average maternal concentrations ranged from 0.06 to 1.0 ng/L in the low category and 1.0 to 19 ng/L in the high category; average childhood concentrations ranged from 0.05 to 2.4 ng/L in the low category and 3.2 to 9.2 ng/L in the high category. For the Leukemia/Lymphoma analysis, average maternal concentrations ranged from 0.1 to 6.4 ng/L in the low category and 10 to 19 ng/L in the high category; average childhood concentrations ranged from 0.07 to 3.4 ng/L in the low category and 5.3 to 9.2 ng/L in the high category.

Duration of Exposure

Duration of potential exposure to TCE was also evaluated and calculated as the number of months with an estimated non-zero TCE concentration. Duration of exposure to TCE, whether during the maternal or childhood exposure periods, was not significantly associated with the odds of childhood cancer (p-values > 0.60). However, when duration variables were included in logistic regression models evaluating average TCE concentration as a predictor of childhood cancer, the associated odds ratios were

moderately increased for estimated maternal TCE concentrations. None of the results were statistically significant with the lowest *p*-value observed being 0.18 for the high category of TCE concentration in the model adjusting for total time of Wilmington residence (OR = 6.9; 95% CI: 0.4-119). Results for childhood TCE concentrations remained mostly unchanged when models were adjusted for duration of exposure. Leukemia/Lymphoma subgroup results for TCE concentrations were not adjusted for duration due to small sample sizes.

Bottled Water Usage during Maternal Exposure Period

Table 15. presents information about the use of bottled water during the maternal exposure period. Based on information collected during interviews, case mothers were approximately twice as likely to report using bottled water as the primary source of home drinking water compared to control mothers (39% vs. 20%). Among the Leukemia/Lymphoma subgroup, a similar pattern was observed with 46% of case mothers, but only 24% of control mothers, reporting bottled water as the primary source of home drinking water. Similarly, for those in the TCE analysis, 44% of case mothers and only 26% of control mothers reported primarily drinking bottled water.

Table 15. Reported use of bottled water as the primary source of home drinking water by mothers during the year before child's birth among participants of the Wilmington Cancer Study, 1972-2000

Primary home drinking water source	All Cancers				Leukemia/Lymphoma			
	Cases (n=18)		Controls (n=74)		Cases (n=11)		Controls (n=45)	
NDMA Study Population	#	%	#	%	#	%	#	%
Tap Water	5	28%	33	45%	3	27%	17	38%
Bottled Water	7	39%	15	20%	5	46%	11	24%
Non-Resident[a]	6	33%	26	35%	3	27%	17	38%
	Cases (n= 16)		Controls (n=57)		Cases (n=10)		Controls (n=39)	
TCE Study Population	#	%	#	%	#	%	#	%
Tap Water	3	19%	20	35%	2	20%	13	33%
Bottled Water	7	44%	15	26%	5	50%	11	28%
Non-Resident[a]	6	38%	22	39%	3	30%	15	38%

[a]Mothers who did not reside in Wilmington during the year before their child's birth.

NDMA and Childhood Cancer, Maternal Bottled Water Use Adjusted

When mothers were assigned zero values for NDMA during months that they primarily drank bottled water, the association between NDMA concentrations in drinking water and the odds of a childhood cancer diagnosis largely disappeared (see Table 16. and Figure 16). In contrast, when mothers were assigned 49% of modeled NDMA values during months that they primarily drank bottled water, the association between NDMA concentrations in drinking water and the odds of childhood cancer were once again apparent, but there was no clear dose-response trend. Instead of odds ratios that increase from the zero to low to high concentration categories, odds ratios were highest for the low concentration category. In the All Cancers analysis, the high concentration category was not associated with childhood cancer and in the Leukemia/Lymphoma analysis, the high category odds ratio was modestly elevated (OR = 1.7; 95% CI: 0.3-9.8). Nevertheless, the estimated higher odds of childhood cancer among those in the low category was statistically significant for the All Cancers analysis (OR = 4.4; 95% CI: 1.1-18) and very close to statistical significance for the Leukemia/Lymphoma subgroup (OR = 5.0; 95% CI: 0.97-26) (Table 16. and Figure 16).

Table 16. Maternal average estimated concentration of NDMA in drinking water (zero, low, high), after accounting for reported bottled water usage, and odds of childhood cancer among children living in Wilmington, MA, 1974-2000

All Cancers	Cases (n=18)		Controls (n=74)				
	n	(%)	n	(%)	OR[a]	95% CI[b]	p-value
Bottled Water = 0							
Zero	14	(78%)	58	(78%)	1.0	-ref-	
Low	3	(17%)	7	(9%)	1.0	(0.2, 5.1)	0.97
High	1	(6%)	9	(12%)	1.1	(0.2, 5.5)	0.88
Bottled Water = 49%							
Zero	9	(50%)	49	(66%)	1.0	-ref-	
Low	7	(39%)	10	(14%)	4.4	(1.1, 18)	0.04
High	2	(11%)	15	(20%)	1.0	(0.2, 5.2)	1.00
Leukemia/Lymphoma	Cases (n=11)		Controls (n=45)				
	n	(%)	n	(%)	OR[a]	95% CI[b]	p-value
Bottled Water = 0							
Zero	8	(73%)	35	(78%)	1.0	-ref-	
Low	2	(18%)	5	(11%)	1.6	(0.3, 9.2)	0.59
High	1	(9%)	5	(11%)	0.8	(0.1, 7.2)	0.87
Bottled Water = 49%							
Zero	4	(36%)	29	(64%)	1.0	-ref-	
Low	5	(45%)	7	(16%)	5.0	(0.97, 26)	0.05
High	2	(18%)	9	(20%)	1.7	(0.3, 9.8)	0.57

[a]OR = Matched Odds Ratio
[b]95% CI = 95% Confidence Interval

Figure 16. Odds ratios and 95% confidence intervals for the association between childhood cancer and average estimated NDMA concentrations in maternal drinking water during the year before birth, after adjustment for reported bottle water usage.
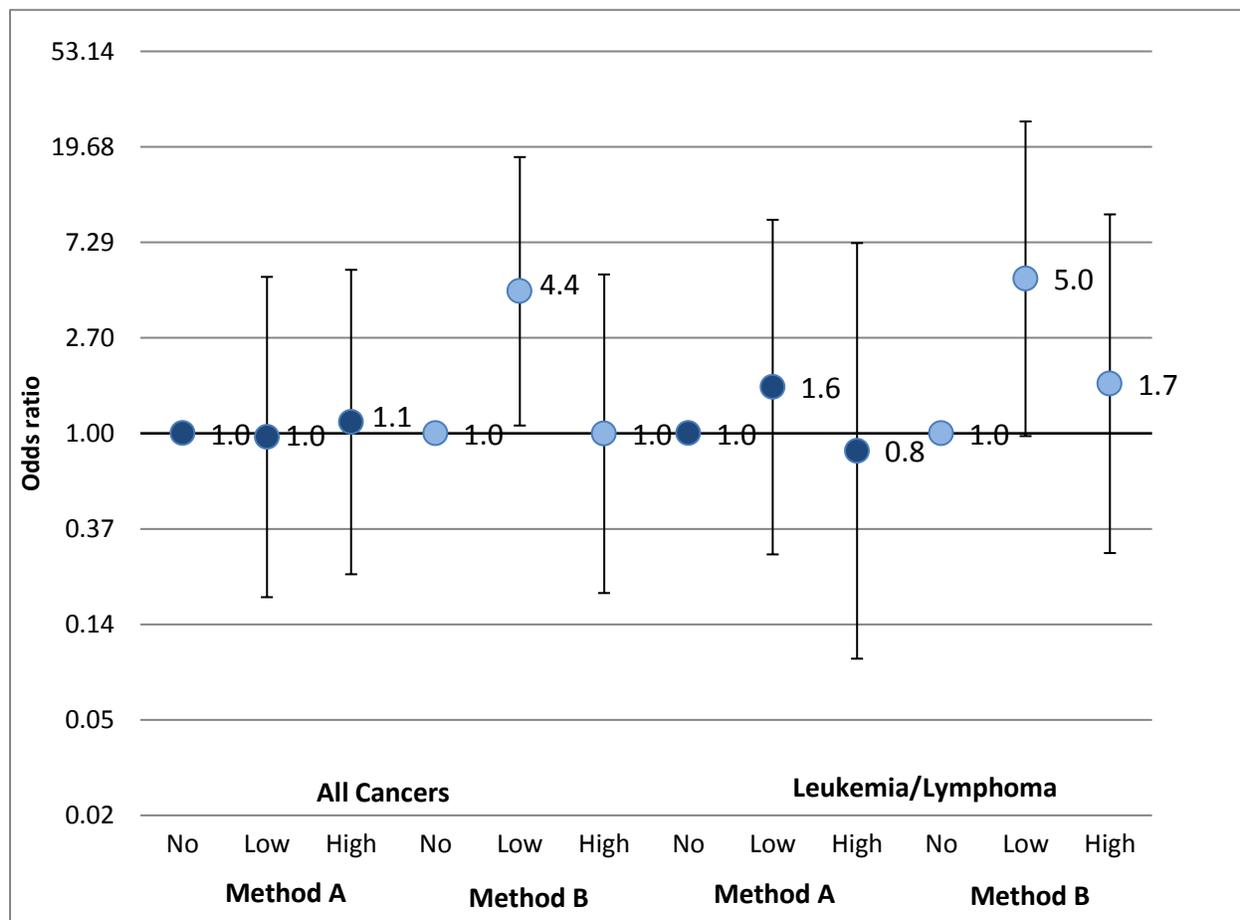
Method A: Zero assigned for NDMA concentration during months when bottled water reported as primary drinking water source

Method B: Forty-nine percent (49%) of modeled value assigned for NDMA concentration during months when bottled water reported as primary drinking water source

<u>TCE and Childhood Cancer, Maternal Bottled Water Use Adjusted</u>
Compared to the un-adjusted analysis, when mothers were assigned zero values for TCE during months that they primarily drank bottled water, the association between TCE concentrations in drinking water and the odds of a childhood cancer diagnosis changed such that an elevated OR was observed in the high concentration category (OR = 2.4; 95% CI: 0.3-18) rather than the low concentration category, and the association continued to lack statistical significance (Table 17. and

Table 14.). When mothers were assigned 49% of modeled NDMA values during months that they primarily drank bottled water, results were identical to the unadjusted analysis for the All Cancers group (Table 17. and

Table 14.). For the Leukemia/Lymphoma subgroup, odds ratios could not be calculated after adjusting for bottled water use due to insufficient data (Table 17.).

Table 17. Maternal average estimated concentration of TCE in drinking water (zero, low, high), after accounting for reported bottled water usage, and odds of childhood cancer among children living in Wilmington, MA, 1981-2000

All Cancers	Cases (n=16)		Controls (n=57)		OR[a]	95% CI[b]	*p*-value
	n	(%)	n	(%)			
Bottled Water = 0							
Zero	13	(81%)	48	(84%)	1.0	-ref-	
Low	1	(6%)	5	(9%)	0.8	(0.1, 8.2)	0.85
High	2	(13%)	4	(7%)	2.4	(0.3, 18)	0.38
Bottled Water = 49%							
Zero	11	(69%)	43	(75%)	1.0	-ref-	
Low	3	(19%)	7	(12%)	4.2	(0.3, 51)	0.26
High	2	(13%)	7	(12%)	1.3	(0.1, 13)	0.81

Leukemia/Lymphoma	Cases (n=10)		Controls (n=39)		OR[a]	95% CI[b]	*p*-value
	n	(%)	n	(%)			
Bottled Water = 0							
Zero	8	(80%)	33	(85%)	1.0	-ref-	
Low	0	(0%)	4	(10%)	NC	NC	NC
High	2	(20%)	2	(5%)	NC	NC	NC
Bottled Water = 49%							
Zero	7	(70%)	30	(77%)	1.0	-ref-	
Low	1	(10%)	5	(13%)	1.0	(0.1, 11)	0.97
High	2	(20%)	4	(10%)	NC	NC	NC

[a]OR = Matched Odds Ratio
[b]95% CI = 95% Confidence Interval
NC = Not calculable due to insufficient data (i.e. few discordant pairs)

Multivariate Exposure Models: NDMA and TCE

NDMA and TCE in Drinking Water and Childhood Cancer
Focusing on maternal exposure, the associations of each drinking water contaminant and the odds of childhood cancer were further evaluated by including dichotomous (ever/never) exposure variables for NDMA and TCE in a logistic regression model together (Table 18.). Results of two combined exposure measures are also presented in Table 18. . These include a dichotomous combined measure (ever NDMA or TCE vs. neither) and a three level combined exposure measure (no exposure, NDMA alone, and

both TCE and NDMA). All results presented in Table 18. are restricted to the 73 study participants with TCE exposure estimations.

In the All Cancers analysis, when both contaminants are included in a model together, the effect estimates of each are somewhat diminished compared to crude model results (NDMA ORs = 1.2 adjusted vs. 1.8 crude; TCE ORs = 1.9 adjusted vs. 2.3 crude). While remaining positively associated with childhood cancer, the associations are not statistically significant and confidence intervals are wide. In the dichotomous combined exposure measure, results are identical to the crude NDMA model because, as shown in Table 12, all mothers estimated to have been exposed to TCE were also estimated to have had NDMA exposure so the combined measure provides no new information. Similarly, in the three-level combined measure, the OR for those estimated to have been exposed to both contaminants are identical to the crude TCE results. Essentially, it is impossible to evaluate the effect of TCE alone, but it's possible to see that the OR is higher for those exposed to both contaminants (OR = 2.3) compared to those exposed to NDMA alone (OR = 1.2).

In the Leukemia/Lymphoma subgroup analysis, inclusion of both contaminants in the same model results in an increased effect estimate for NDMA (ORs = 2.4 adjusted vs. 1.9 crude) whereas the effect estimate for TCE is diminished and no longer positive (ORs = 0.7 adjusted vs. 1.7 crude). Just as in the All Cancers analysis, the dichotomous combined exposure measure is identical to the crude NDMA model because no one was estimated to have been exposed to TCE alone. In the three-level combined measure, in contrast to the All Cancers analysis, the OR for exposure to NDMA alone (OR = 2.4) is higher than the OR for those estimated to have been exposed to both contaminants (OR = 1.7).

Table 18. Presence of NDMA and TCE in maternal residential drinking water and odds of childhood cancer among children living in Wilmington, MA, 1974-2000 (n=73).

All Cancers	Cases	(n=16)	Controls	(n=57)			
	n	(%)	n	(%)	OR[a]	95% CI[b]	*p*-value
Crude NDMA							
Ever vs. Never	8	(50%)	24	(42%)	1.8	0.5-6.2	0.37
Crude TCE							
Ever vs. Never	5	(31%)	14	(25%)	2.3	0.5-12	0.32
Multivariate							
Ever NDMA vs. Never	8	(50%)	24	(42%)	1.2	0.2-8.7	0.86
Ever TCE vs. Never	5	(31%)	14	(25%)	1.9	0.2-25	0.62
Dichotomous Combined Measure							
No Exposure	8	(50%)	33	(58%)	1.0	-ref-	
NDMA or NDMA and TCE	8	(50%)	24	(42%)	1.8	0.5-6.2	0.37
Three-level Combined Measure							
No Exposure	8	(50%)	33	(58%)	1.0	-ref-	
NDMA alone	3	(19%)	10	(18%)	1.2	0.2-8.7	0.86
NDMA and TCE	5	(31%)	14	(25%)	2.3	0.5-12	0.32

Leukemia/Lymphoma	Cases	(n=10)	Controls	(n=39)			
	n	(%)	n	(%)	OR[a]	95% CI[b]	*p*-value
Crude NDMA							
Ever vs. Never	6	(60%)	16	(41%)	1.9	0.5-8.2	0.37
Crude TCE							
Ever vs. Never	3	(30%)	9	(23%)	1.7	0.3-11	0.55
Multivariate							
Ever NDMA vs. Never	6	(60%)	16	(41%)	2.4	0.2-27	0.49
Ever TCE vs. Never	3	(30%)	9	(23%)	0.7	0.04-15	0.85
Dichotomous Combined Measure							
No Exposure	4	(40%)	23	(59%)	1.0	-ref-	
NDMA or NDMA and TCE	6	(60%)	16	(41%)	1.9	0.5-8.2	0.37
Three-level Combined Measure							
No Exposure	4	(40%)	23	(59%)	1.0	-ref-	
NDMA alone	3	(30%)	7	(18%)	2.4	0.2-27	0.49
NDMA and TCE	3	(40%)	9	(23%)	1.7	0.3-11	0.55

[a]OR = Matched Odds Ratio
[b]95% CI = 95% Confidence Interval

Multivariate Models: Adjusting for Risk Factors

The effect of possible confounding on the associations between childhood cancer and exposure to NDMA and TCE was evaluated for each of eleven individual covariates: 1) oxygen given after birth, 2) incubator use after birth, 3) low birth weight, 4) adverse birth event, 5) prenatal ultrasound, 6) antihistamine use by the child, 7) metals, alloys, or solder exposure, 8) plastics, synthetics, or resins exposure, 9) exhaust fume exposure, 10) herbicide exposure, and 11) maternal occupational exposure to ionizing radiation. These variables all had elevated odds ratios and *p*-values that were <0.20 for the association with all cancers or with leukemia/lymphoma. A variable was considered to be acting as a confounder if the effect estimates for exposure changed by at least 10% when the covariate was included in the model. Confounding was evaluated in models of association between both the All Cancers group and the Leukemia/Lymphoma sub-group for maternal NDMA exposure measured as dichotomous (ever/never) and as categorical (zero, low, high) average modeled NDMA concentrations in drinking water. Due to sample size considerations, TCE exposure analyses were evaluated for confounding only among the All Cancers group and only using dichotomous (ever/never) modeled TCE concentrations in maternal drinking water. Confounding was not evaluated in models with multiple covariates due to sample size limitations.

In all adjusted models, potential exposure to NDMA in maternal drinking water remained positively associated with childhood cancer (all cancers and leukemia/lymphoma). For the analysis of categorical maternal NDMA concentrations and all cancers, eight of the eleven variables were determined to be confounders. Due to varying amounts of missing information across covariates, crude models were also re-run to evaluate effects within the sample of participants having complete information for each covariate. To highlight the impact that each covariate had on the effect estimates for NDMA,

Table 14. presents the new crude ORs for NDMA alongside the adjusted ORs for each multivariate model. In summary, crude ORs for the effect of high NDMA concentrations compared to no estimated exposure to NDMA ranged from 2.4 to 3.3 and adjusted ORs for this comparison ranged from 2.5 to 3.9.

Similarly modest changes were observed in adjusted models for the dichotomous (ever/never) maternal NDMA exposure in the All Cancers group with only four variables found to be acting as confounders (oxygen given after birth, incubator use after birth, low birth weight, and prenatal ultrasound). Crude ORs ranged from 1.7 to 2.7 compared to adjusted ORs of 1.6 to 2.4. In the Leukemia/Lymphoma subgroup analysis, sample size limitations and lack of discordant pairs inhibited evaluation of some variables as confounders, including low birth weight, prenatal ultrasound, and metals, alloys, or solder exposure; adverse birth event was evaluated in the ever/never analysis for the Leukemia/Lymphoma subgroup, but not in the categorical exposure analysis. In all, six variables were found to act as confounders of the categorical NDMA results and five variables impacted the dichotomous (ever/never) NDMA results. Crude and adjusted ORs ranged from 2.5 to 3.6 and 1.6 to 3.7, respectively, for dichotomous (ever/never) maternal exposure to NDMA and odds of leukemia/lymphoma. For the categorical analysis, high compared to no estimated maternal NDMA concentrations resulted in crude and adjusted ORs ranging from 4.6 to 11 and 4.0 to 16, respectively, for the odds of leukemia/lymphoma. Four variables were found to be confounders of the association between dichotomous (ever/never) exposure to TCE and childhood cancer with crude and adjusted ORs ranging from 2.0-2.3 and 1.9 to 2.8, respectively. Detailed results of all confounding analyses are presented in Appendix E.

Table 19. Odds ratios and 95% confidence intervals for the association between NDMA in drinking water and any childhood cancer following adjustment for confounding variables

All Cancers	Crude		Adjusted	
Maternal Exposure	OR[a]	95% CI[b]	OR[a]	95% CI[b]
Oxygen After Birth (n=77)				
NDMA Low vs. Zero	1.4	(0.3 - 7.7)	1.1	(0.1 - 9.0)
NDMA High vs. Zero	2.9	(0.6 - 15)	3.9	(0.7 - 23)
Incubator at Birth (n=83)				
NDMA Low vs. Zero	1.2	(0.2 - 6.1)	0.9	(0.2 - 4.9)
NDMA High vs. Zero	2.4	(0.5 - 11)	2.5	(0.5 - 11)
Low Birth Weight (n=85)				
NDMA Low vs. Zero	1.2	(0.2 - 6.4)	1.7	(0.3 - 9.6)
NDMA High vs. Zero	2.6	(0.6 - 11)	3.4	(0.7 - 17)
Adverse Birth Event (n=80)				
NDMA Low vs. Zero	1.5	(0.3 - 7.8)	1.0	(0.1 - 7.2)
NDMA High vs. Zero	3.0	(0.6 - 15)	3.6	(0.7 - 20)
Household Plastics/Glues Exposure (n=90)				
NDMA Low vs. Zero	1.4	(0.3 - 6.6)	1.2	(0.2 - 5.8)
NDMA High vs. Zero	2.9	(0.8 - 10)	3.3[†]	(0.9 - 12)
Household Metals/Solder Exposure (n=91)				
NDMA Low vs. Zero	1.4	(0.3 - 6.7)	1.1	(0.2 - 5.6)
NDMA High vs. Zero	2.9	(0.8 - 10)	2.8	(0.8 - 9.8)
Prenatal Ultrasound (n=85)				
NDMA Low vs. Zero	1.2	(0.2 – 6.0)	1.0	(0.2 - 5.1)
NDMA High vs. Zero	3.3	(0.8 - 13)	2.9	(0.7 - 12)
Occupational Ionizing Radiation, Maternal (n=91)				
NDMA Low vs. Zero	1.3	(0.3 - 6.0)	1.5	(0.3 - 7.3)
NDMA High vs. Zero	3.0	(0.8 - 10)	2.7	(0.7 - 9.8)

*Note: Sample sizes vary between models due to missing covariate data for some children.
[a]OR = Matched Odds Ratio
[b]95% CI = 95% Confidence Interval
†Marginally significant association with the odds of childhood cancer ($p < 0.10$)
‡Statistically significant association with the odds of childhood cancer ($p < 0.05$)

Uncertainty Analyses

As described in the Exposure Assessment section of Methods, two inputs of the groundwater and drinking water distribution system models were found to have some degree of uncertainty capable of causing significant impacts on the resulting NDMA concentration estimates. These two model parameters were the arrival time of NDMA in the DAPL of the MMB aquifer and some supply well pumping rates (particularly during early years of the exposure assessment period when pumping data were limited). To

evaluate the sensitivity of the study's main exposure-outcome results to variations in these model parameters, a series of eight alternative NDMA concentration datasets were produced after varying the values of these two key parameters individually and in combination.

Figure 17. presents the results of the association between average NDMA concentrations in maternal drinking water (zero, low, or high) and development of any childhood cancer using each of the eight alternative exposure datasets and for the base model exposure dataset. In each model, ORs are elevated for the comparison between high versus zero estimated NDMA concentrations in drinking water. All ORs for this comparison are equal to or higher than the base model results of 3.0 (OR range: 3.0 to 4.9) and p-values are in the marginally significant or statistically significant range for all eight models. Changing the NDMA arrival time to 5 years later (+ 5 years) results in the largest ORs for the high concentration category whereas changing the NDMA arrival time to 5 years earlier (- 5 years) and/or changing pumping rates in either direction produces more modest differences compared to the base model. Only one of the alternative models (reducing pumping rates by 20%) produced ORs for the low NDMA concentration category that were above 1.0.

Figure 17. Range of uncertainty in odds ratios for the association between childhood cancer and average estimated NDMA concentrations (zero, low, high) in maternal drinking water (during the year before birth) based on eight alternative exposure simulations.
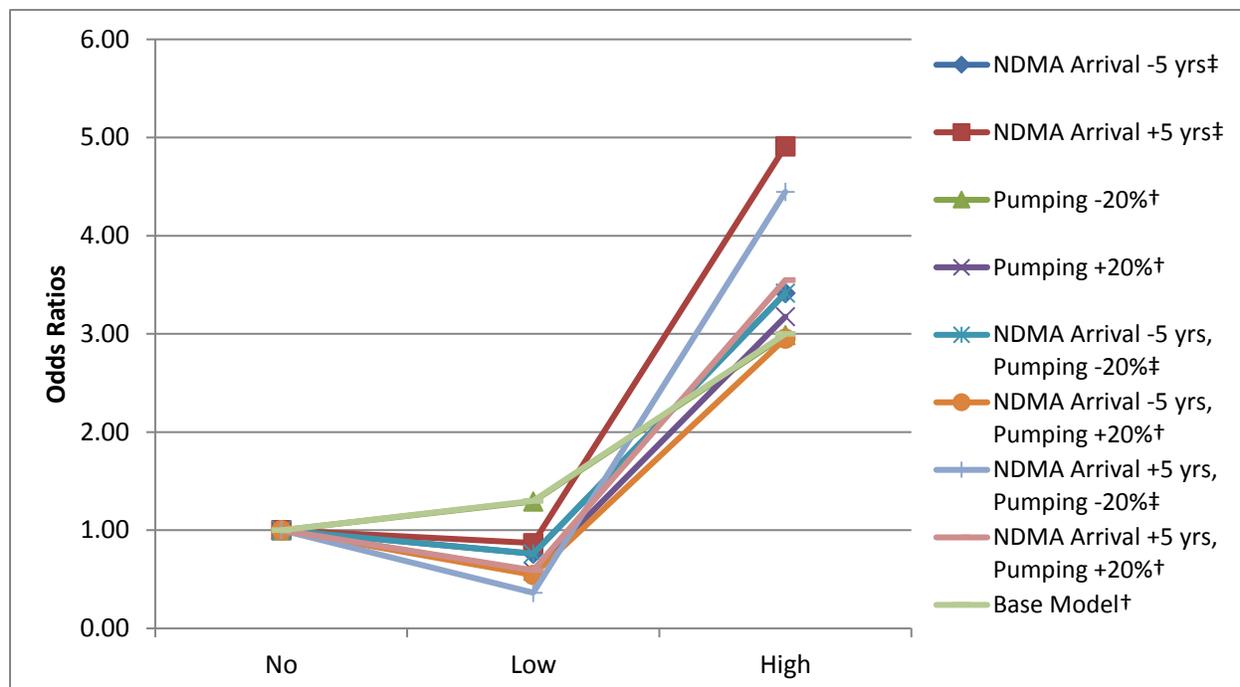
†Marginally significant association with the odds of childhood cancer ($p < 0.10$) for the high concentration category compared to no estimated NDMA in drinking water.
‡Statistically significant association with the odds of childhood cancer ($p < 0.05$) for the high concentration category to no estimated NDMA in drinking water.

Figure 17. presents results for each of the eight alternative exposure datasets when used to evaluate the childhood exposure period and the association between average NDMA concentrations in drinking water (zero, low, or high) and development of any childhood cancer. In general, there is very strong model agreement across all results and very little difference between the base model and the alternative models. No positive association with childhood cancer is observed for estimated NDMA concentrations during the childhood exposure period.

Figure 18. Range of uncertainty in odds ratios for the association between childhood cancer and average estimated NDMA concentrations (zero, low, high) in childhood drinking water based on eight alternative exposure simulations.
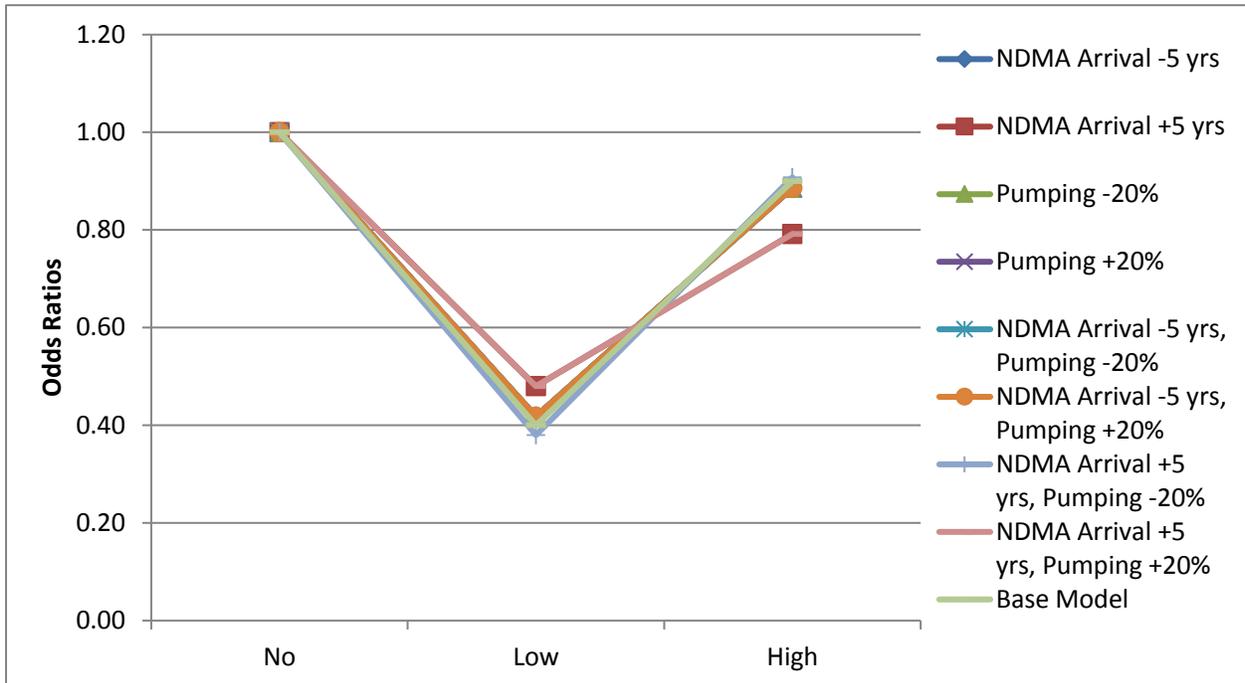
DISCUSSION

INTRODUCTION

In this case-control study, potential environmental exposures were evaluated for their association with childhood cancer diagnosed in Wilmington, MA from 1990-2000. The study faced several challenges including a small sample size, a retrospective exposure assessment, and retrospective ascertainment of additional risk factors. Yet, strong positive associations were observed between contaminants in maternal residential drinking water and childhood cancer. The most compelling results include statistically significantly higher odds of a leukemia or lymphoma diagnosis among children whose mothers lived in homes with the highest estimated n-nitrosodimethylamine (NDMA) concentrations in drinking water compared to children whose mothers were estimated to have had no NDMA exposure during the year before their child's birth (OR = 5.0; 95% CI: 1.0-24). The odds of any cancer diagnosis were also elevated among this group, but with only marginal statistical significance (OR = 3.0; 95% CI: 0.8-11); because leukemia and lymphoma diagnoses made up 60% of the 18 cases in this study, the results of the All Cancers analysis are largely driven by the strong association observed with leukemia/lymphoma. Both associations displayed a dose-response trend, and the trend for the Leukemia/Lymphoma subgroup had a marginally significant p-value of 0.06. Estimated concentrations of trichloroethylene (TCE) in maternal drinking water were also positively associated with odds of any cancer diagnosis, but results were not statistically significant, a dose-response effect was not observed, and the small number of participants with available estimated TCE concentrations prevented deeper analysis of the Leukemia/Lymphoma subgroup.

When those reporting that they primarily drank bottled water were assigned zero exposure, associations between NDMA and childhood cancer were no longer observed. However, when bottled water use was accounted for in exposure assignments by decreasing estimated concentrations to 49% of modeled values, associations between NDMA and childhood cancer were strengthened (though no longer in a dose-responsive fashion). For TCE, accounting for bottled water usage had less of an apparent effect. Increased odds of cancer were not observed in those with higher estimated concentrations of NDMA or TCE during the childhood exposure period.

After evaluating a host of additional demographic and risk factor information collected through interview, increased odds of childhood cancer were also observed among children administered oxygen immediately after birth, those with low birth weight, and those who experienced either of those adverse birth events or placement in an incubator at birth. Two additional risk factors (childhood use of antihistamines and household use of plastics, synthetics, or resins) were positively associated with childhood cancer, but *p*-values were of marginal significance and adjustments were not made for multiple comparisons. When these risk factors, in addition to other selected potential confounders, were adjusted for in multivariate models with NDMA or TCE exposure, the adjustments for confounding did not result in any meaningful change in the ORs or in the interpretation of the results.

> **Multiple Comparisons**
>
> The issue of multiple comparisons arises when a large number of statistical tests are conducted—for instance, when evaluating the associations of many potential risk factors and a disease outcome of interest. Each additional test or comparison increases the likelihood that a "significant" association will occur simply due to chance. To compensate for this issue, a more stringent threshold for statistical significance can be applied.

The objective of this study was to obtain an explanation for the pattern of childhood cancer in Wilmington, MA between 1990 and 2000. Specifically, childhood cancer rates were higher than would be expected and appeared to occur more frequently in certain areas of the town. The study was maximally designed to consider available risk factor data, given the relatively small number of children with cancer, by using multiple controls, sophisticated exposure modeling, and detailed personal interviews. The study result risk estimates were not precise, but the associations suggested with past NDMA and/or TCE drinking water exposures offer what we believe is a plausible explanation, supported by valid objective data, for the pattern of elevated cancer observed in areas of Wilmington, MA. The presence of these contaminants cannot definitively explain the pattern of childhood cancer, but it should be recognized that despite the low statistical power of the study, several findings reported here do reach the traditional threshold of statistical significance, are plausibly supported by the literature, and could be real. However, as in any study, the statistical associations found could have been affected by bias or confounding or could be due to chance. Characteristics of the study population, consistency of the results with scientific literature, and the potential for misclassifying exposure, as well as the impact of other possible biases are herein described and considered to further elucidate the validity of the observed results.

CANCER TYPES

Nine different cancer types are represented among eligible Wilmington childhood cancer cases between 1990 and 2000: leukemias (acute lymphocytic and acute myeloid) (n=8), lymphomas (Hodgkin and non-Hodgkin) (n=3), bone cancer (EFOT, including pPNET) (n=3), germ cell (intracranial/intraspinal) (n=2), CNS (n=1), hepatic (n=1), other malignant epithelial (sweat gland adenocarcinoma) (n=1), renal (n=1), and soft tissue sarcoma (rhabdomyosarcoma) (n=1). Sweat gland adenocarcinoma is the rarest of these tumors, but the intracranial and intraspinal germ cell, EFOT, and hepatic cases are all considered uncommon. The remaining types of tumors observed are among the most common childhood cancer types (Roman 2018). With leukemia and lymphoma diagnoses making up 60% of the 18 cases in this study, the results of the All Cancers analysis appear to be largely driven by the strong associations observed with leukemia/lymphoma. However, the presence of only one or two cases of any specific cancer type precludes a conclusive evaluation of the non-leukemia or non-lymphoma cancer types and the risk factors investigated, including exposure to drinking water contaminants. Leukemias and lymphomas are different types of cancer (leukemia is a cancer of the blood and lymphoma is a cancer of the lymphatic system), but they both result in the malignant transformation of cells destined to be lymphocytes. The principal reason for combining them in this analysis was due to similar environmental risk factors, such as exposure to pesticides, in the published literature (Chen et al. 2015; Infante-Rivard and Weichenthal 2007; Zahm and Ward 1998).

Sometimes the types and subtypes of cancer or the ages of diagnosis can appear inconsistent with the scientific literature, thereby suggesting the possibility of some unusual causal factor(s) at play. In the Wilmington population, as noted, there were several examples of somewhat different than expected types of childhood cancer (sweat gland adenocarcinoma, intracranial/intraspinal germ cell tumors, EFOT, and hepatic cancer). With the small numbers of cases of each, however, it is impossible to evaluate whether any individual diagnosis was due to chance or some other factor(s). Uncommon cancer types do arise occasionally and the occurrence of individual cases should be interpreted with caution. There are no established environmental risk factors for most of these cancers in the literature, though research is frequently lacking or inconsistent. There is some evidence that hepatoblastoma may be associated with parental exposure to tobacco smoke, oil products, paints, or metals (IARC 2012; Buckley et al. 1989; Janitz et al. 2017), but more research is needed. Sweat gland adenocarcinoma case reports suggest that previous radiotherapy and exposure to ultra violet radiation (e.g., sun exposure) may increase risk (Gordon et al. 2017), but no research has been done to confirm the associations.

Other than those noted, the types and subtypes of cancer diagnosed in Wilmington children during this period were among those that occur most commonly, and the ages at diagnosis for all cancers seen, including the less common types, appear consistent with what is reported in the scientific literature. For example, among children with leukemia, generally 76% are acute lymphocytic leukemias (ALL), which is the same proportion found in the Wilmington study population (MCR 2014). Peak occurrence of ALL occurs between the ages of two and four, with the majority of cases in children less than 10 years old. Four of the six Wilmington children were diagnosed within the two-four year age group (the others at ages seven and eight). Most lymphomas are diagnosed in teenagers, as were the Wilmington children (ACS 2014). The most common type of kidney cancer is Wilm's tumor occurring usually in children under five years of age (Ries et al. 1999). This is consistent with the age at diagnosis of the child diagnosed with Wilms tumor. Similarly, the type of liver cancer (hepatoblastoma) and age at diagnosis (in children less than five) of the child in Wilmington is typical for this type of cancer (MCR 2014; Roman et al. 2018).

N-NITROSODIMETHYLAMINE (NDMA) AND CHILDHOOD CANCER

There is ample evidence in published literature on the plausibility of NDMA causing cancer. Although considered a probable human carcinogen by both the US EPA and IARC (IARC 1978, 1987; US EPA 2017), most toxicity information for NDMA has come from laboratory testing and animal studies. Available human studies have been more limited and focus mostly on adults. No studies have been found that examine cancer risk from NDMA through drinking water.

NDMA is known to be genotoxic and mutagenic (WHO 2008), meaning that it can create changes to DNA that can lead to cancer in different ways. In rats, mice, and hamsters, NDMA has been shown to be a transplacental carcinogen (CalEPA 2006), meaning that the placenta acts as a transmission route by which pregnant animals transmit the toxin to their offspring who then develop cancer. In a laboratory study of human placentas and NDMA, it was demonstrated that transplacental transmission of NDMA can occur in humans (Annola et al. 2009).

NDMA is part of a group of compounds known as nitrosamines, which are collectively thought to be carcinogenic. Studies of other nitrosamines can help provide clues to the toxicity of NDMA. Most existing research in humans has focused on exposure to NDMA from dietary sources such as cured meats or beer, or on exposure to nitrite, nitrate, and *n*-nitroso compounds in general. Case-control studies have suggested an association between ingestion of NDMA from food sources and the risk of gastric and lung cancers in adults (De Stefani et al. 1996; González et al. 1994; Goodman et al. 1992; La Vecchia

et al. 1995; Pobel et al. 1995; Risch et al. 1985; Rogers et al. 1995). Case-control studies have also found an increase in the risk of childhood brain tumors with maternal dietary exposure to *n*-nitroso compounds, but results suggest that risk is modified by other nutrients and genetic factors (Huncharek and Kupelnick 2004; Johnson et al. 2014).

TRICHLOROETHYLENE (TCE) AND CHILDHOOD CANCER

TCE is characterized as carcinogenic in humans by EPA (2011), reasonably anticipated to be a carcinogen by NTP (2011), and carcinogenic to humans by IARC (Guha et al. 2012; IARC 2014). Epidemiological studies provide strong evidence that trichloroethylene can cause kidney cancer in humans and some evidence that it causes non-Hodgkin lymphoma and liver cancer. While most studies evaluate adult worker populations, children are expected to have similar health effects as adults (ATSDR 2019). Epidemiological data on associations between TCE exposure and childhood cancer is limited, but some community-based studies have produced results suggestive of an effect. Limitations of these studies prevent definitive conclusions to be drawn, but increased incidence of childhood leukemia was reported after ingestion of TCE-contaminated well water in Woburn, MA (Costas et al. 2002) and childhood leukemia, ALL, and non-Hodgkin lymphoma were elevated after exposure to TCE and other compounds in New Jersey (Fagliano et al. 2003).

Evidence of a causal association between TCE exposure and kidney cancer in adults, on the other hand, is strong and convincing based on occupational cohort and case-control studies. There is also some evidence, though limited to a few occupational cohort studies, for increased risks of non-Hodgkin lymphoma and liver cancer (ATSDR 2019).

CARCINOGENIC EXPOSURES IN-UTERO

Given that there may be different risks of cancer from exposure at different stages of human development, we examined the risk of childhood cancer by looking at two different exposure windows: from embryo to birth and from birth through adolescence. Just as a child's smaller mass means that they experience a much greater dose of exposure relative to their size than an adult experiences (WHO 2008), so too does a fetus experience a greater relative dose than a child. The fetus may also be more susceptible to effects from environmental exposures due to the rapid growth and development of different organ systems during the *in utero* period. In a previous study in Woburn, Massachusetts, MDPH investigators observed a similar finding of an increased risk of leukemia from *in utero* exposure via pregnant mothers who drank water contaminated with a mixture of chemicals, including TCE (Costas et al. 2002). NDMA was not a suspected contaminant in that study. More recently, the US Agency for

Toxic Substances and Disease Registry (ATSDR) published results in 2013 of a drinking water study conducted at Camp Lejeune in North Carolina (Ruckart 2013). Drinking water contaminants included TCE, tetrachloroethylene (PCE), benzene, vinyl chloride, and trans-1,2-dichloroethylene (DCE). Associations were found between *in utero* drinking water exposures and neural tube defects. Positive odds ratios ranging from 1.5-1.6 were observed for associations between childhood cancer and three contaminants (PCE, DCE, and vinyl chloride). However, the associations were not supported by a dose-response relationship and had wide confidence intervals with *p*-values of 0.4. Finally, in a meta-analysis of fetal exposure to NDMA from maternal ingestion of cured meats, a statistically significant increased risk of childhood brain cancer was observed (Huncharek and Kupelnick 2004); despite limitations, the study results support a causal association between exposure to *n*-nitroso compounds through ingestion during pregnancy and subsequent childhood brain tumor in the offspring.

EXPOSURE ASSESSMENT

The Woburn, MA and Camp Lejeune, NC studies mentioned above used sophisticated drinking water modeling to estimate historical exposure to drinking water contaminants. Similarly, the NDMA values presented in this study are the result of three water models: one simulated groundwater flow within the Maple Meadow Brook (MMB) aquifer; one simulated the fate and transport of NDMA through the aquifer to municipal wells; and one model simulated the distribution of treated water contaminated with NDMA through the water distribution system to residences throughout the town of Wilmington. TCE exposure was estimated using only the latter of these models because contamination sources within the aquifer were unknown, but measured concentrations in treated water were available. These models were based on the hydrogeology characterizing the Olin Chemical hazardous waste site and underlying MMB aquifer; available data on contaminant sources, fate, and transport in the aquifer; the chemistry of NDMA; US EPA environmental data; historical water testing data; historical pumping rates of 10 municipal wells located throughout Wilmington; and the structure of the municipal water distribution system network. Those conducting water modeling were blinded as to the addresses of cases and controls.

The accuracy of numerical modeling applications relies heavily on the quality of data used for key parameters as well as the validity of inherent modeling assumptions. Based on the availability of data from extensive environmental investigations of the Olin Chemical site and underlying aquifer, there is a high degree of confidence in the reliability of the representation of the groundwater system (see Appendix C for details). However, some uncertainty exists with regards to certain parameters of the water transport and water distribution system models. For example, while every effort was

made to re-create the monthly pumping rates at each well during the years of the study period, there were periods of time for which rates of flow at individual municipal wells were not measured or recorded by the town. In particular, pumping rates prior to 1989 were estimated based on individual well capacities, even though the wells may not have been used in proportion to their hydraulic capacity. In addition, during periods of the study years for which measurements were available, the quality of those records was sometimes inconsistent due to some mechanical failures in the pumping rate meters.

As reported in Appendix C, a qualitative and quantitative uncertainty analysis was performed which identified two important model parameters whose uncertainty was found to impact estimated concentrations of NDMA in the town's drinking water to an appreciable degree. In addition to the pumping rates prior to 1989, the other important area of uncertainty relates to the timing of NDMA arrival to source areas within the MMB aquifer. The hypothesized 1972 arrival time of the DAPL source within the Western Bedrock Valley represents a best judgment and is supported by transport calculations from the Olin Chemical site to the area of DAPL accumulation. However, the absence of NDMA measurements in the MMB aquifer near the present-day DAPL source in the Western Bedrock Valley make the arrival times of both the DAPL source and subsequent NDMA capture by the water supply wells uncertain.

The quantitative analysis generated uncertainty ranges for the simulated monthly NDMA concentrations at each location in the water distribution system after varying each parameter individually and in combination (moving the NDMA arrival time by 5 years in both directions and changing pumping rates by 20% in both directions). Results showed that varying the two uncertainty inputs could result in large changes in the magnitude and spatial penetration of NDMA in the Wilmington drinking water distribution system primarily from 1974 to 1979, to a lesser extent from 1981 to 1989, and not at all after 1989. From 1990 through 2003, the simulated concentrations show no change from baseline.

As presented in Results, the uncertainty analyses were carried through to the final exposure-outcome models by evaluating NDMA concentrations (as zero, low, or high) and the odds of childhood cancer using each of the eight alternative exposure datasets created after varying the two parameters within their estimated ranges of uncertainty. Overall, results were very similar to those presented using the baseline exposure dataset with ORs for the high maternal exposure category ranging from 3.0 to 4.9 (all p-values <0.10 and some models having p-values <0.05) and ORs for the low maternal exposure category ranging from 0.4 to 1.3. Childhood exposure models were even more consistent across the eight analyses and continued to show no positive association between NDMA concentrations and childhood cancer. So, although existing uncertainty in key

groundwater and distribution system model parameters was found to impact estimated NDMA concentrations, these changes were not enough to have any meaningful impact on the associations measured using the baseline exposure model.

Unmeasured Sources of NDMA Exposure

To further complicate the issue of NDMA exposure is the fact that NDMA is present in everyday products. The primary sources of human NDMA exposure are tobacco smoke, chewing tobacco, toiletry and cosmetic products like shampoo and cleansers, interior air of cars, and various other household goods, such as detergents and pesticides. The major pathway of exposure to NDMA is ingestion of certain foods like cured meats (particularly bacon), beer, fish, cheese, and other food items (ATSDR 1999). In the Wilmington study, no dietary history was obtained due to the fact that NDMA exposure was not identified as a hypothesized exposure in Wilmington until after the interviews had been conducted. Therefore, we do not know the extent or pattern of exposure to NDMA through diet among the study participants. While it is possible that consumption of these foods differed between cases and controls or between those with higher and lower NDMA exposures from drinking water, it is most likely that the pattern of consumption was non-differential. Therefore, not controlling for NDMA exposure through the diet most likely makes it more difficult to detect an association with NDMA in drinking water in this study (i.e. it would bias our results towards the null).

Exposure Metric

In this study, modeled concentrations of NDMA and TCE in drinking water mains at each residential address were used as a surrogate for potential exposure. Specifically, the primary exposure metric consisted of the average of all non-zero monthly contaminant concentrations modeled for each participant address for the duration of residency. Due to limitations in the questionnaire design, detailed exposure calculations incorporating a person's daily water intake were not conducted. A benefit of this simplified approach is that it simultaneously accounts for exposure via both ingestion and inhalation routes (e.g. during showering), but a limitation is that it assumes similar water consumption and showering habits by each participant. This assumption would tend to bias results towards the null unless water usage habits were coincidentally different in a systematic way between cases and controls, which seems unlikely. However, while detailed consumption habits were unavailable, participants were asked whether their primary drinking water source for a particular residence was tap water, filtered tap water, or bottled water. Interestingly, the percentage who reported bottled water as their primary drinking water source was nearly twice as high for case mothers compared to control mothers (39% vs. 20%). This issue is explored further in the following section on information bias.

Estimated contaminant concentrations were averaged across two different time periods representing two potential etiologies of disease, the *in-utero* time period and the childhood time period. This average measure is primarily an evaluation of concentration magnitude and does not measure the potential effect of exposure duration. For this reason, duration of exposure was also evaluated as an independent predictor of childhood cancer both in univariate logistic regression models and as a covariate in models with the primary exposure metric. Duration of exposure was not found to be independently associated with childhood cancer and it was not found to impact associations between the primary exposure metric (average monthly contaminant concentrations) and childhood cancer.

Potential exposure was also evaluated as an ever/never type metric, in addition to a categorical zero/low/high metric, which may be useful if any amount of exposure to NDMA or TCE is thought to increase risk of childhood cancer. A dichotomous ever/never metric can also be useful when a relatively high degree of confidence exists around the presence or absence of exposure even if precise exposure estimates have potential error (such as from lack of ingestion information). In the ever/never analysis, the odds ratios were elevated for maternal NDMA exposure and the risk of childhood cancer as well as the risk of leukemia/lymphoma, although the elevations were not statistically significant.

RESPONSE RATES/SELECTION BIAS

Three of the 21 eligible children diagnosed with cancer in Wilmington did not participate in this study, representing one bone cancer, one germ cell cancer, and one soft tissue sarcoma. Only limited information is known about the location and duration of their residence and no information known on medical histories or other potential risk factors. The main impact of their lack of inclusion would be a smaller sample size and the related reduction in the study's statistical power to reject or accept hypotheses related to environmental exposures and childhood cancer.

The participation rate for controls was 32%. Nonetheless, a large pool of potential controls enabled the study goal of a 1:4 case to control ratio to be met. Thus, the statistical efficiency of the study to detect effects was not reduced by the somewhat low control participation rate. However, there exists the theoretical possibility of some difference(s) between those controls who agreed to participate and those who did not. For an adverse effect on the study's results to occur, the difference(s) would need to be related to their potential for exposure to drinking water contaminants (e.g., if non-participating controls lived in a different part of town than participating controls or for different lengths of time) or in their experience with other childhood cancer risk factors.

There was limited information with which to assess the potential for this bias (i.e. no full residential histories), but a geographic comparison of recruitment letter addresses between participating and non-participating controls showed similar proportions of each within the areas of Wilmington estimated to have received higher concentrations of NDMA and TCE versus those receiving very little of the contaminants. This suggests that control participation was likely not related to the opportunity for exposure to drinking water contaminants.

With respect to other population characteristics, comparisons showed that maternal educational background, length of residence in Wilmington, age at birth, and prenatal vitamin use were all very similar between participating cases and controls. Family history of cancer was also similar between cases and controls with approximately 20% of each having an immediate family member with cancer diagnosed prior to age 50 and only one participant, a control, having an immediate family member with cancer diagnosed prior to age 20 years (rates of missing information for this variable were similar between cases and controls at approximately 15%—see Appendix D). This suggests that the controls did not appear to be systematically different from the cases and that selection bias was not likely introduced into the study.

INFORMATION BIAS

In any study, it is important to consider the potential for information bias and the effect it may have when interpreting the results. Elsewhere in the report, methods are described for the assessment and control of confounding, which can statistically distort an association between an exposure and outcome. Information bias, on the other hand, cannot be readily controlled through statistical analysis, and is better prevented where possible. Exposure misclassification, as previously discussed, is one type of information bias. Thorough historical review of available data and complex modeling were conducted to assign NDMA and TCE concentrations as accurately as possible. Nonetheless, no model is perfect and the possibility of error exists. This type of bias is likely to be non-differential in that the potential exposure misclassification is unlikely to be related to whether one is a case or a control and, therefore, tends to bias results towards an underestimate of association between exposure and outcome.

Another type of information bias is called recall bias, which can result from the inability of people being interviewed to accurately recall information like medical history. Recall bias has been shown in other studies to sometimes be different in cases versus controls. This is differential bias and can result in an underestimate or overestimate of an association depending on the specifics of the recall bias. In this study, we attempted to minimize recall bias by providing an interview guide on the types of information of

interest to participants prior to their interview. This gave both cases and controls the same opportunity to recall facts about their lives. Nevertheless, parents of cases may be prone to more thoroughly comb their memories than unaffected parents to try to recall exposure to factors thought to be possible causes of their child's illness (Linet 2003). This could result in higher reporting by case parents of household exposures such as metals, alloys, or solders; plastics, synthetics, or resins; and herbicides, as well as occupational ionizing radiation exposure during pregnancy.

Another specific type of recall bias, called social desirability bias, may also have affected cases and controls disproportionately. Social desirability bias occurs when a participant's perception of stigma related to sensitive topics leads them to misreport certain information. In this study, it's possible that parents of children with cancer were more likely to misreport a history of smoking or alcohol use, for example, than the parents of controls. Under-reporting of these behaviors is common in most surveys, but parents of cases may have felt particularly uncomfortable disclosing such information, especially if they stopped smoking early in pregnancy or otherwise felt that the behavior was irrelevant to their child's cancer. Indeed, smoking during the year before birth was reported by only 6% of case mothers compared to 27% of control mothers. Though these results may be accurate, they are somewhat unlikely given data on the prevalence of smoking among women during that time. Specifically, the US Office on Smoking and Health reports that approximately 35% of women aged 25-44 were active smokers in 1979 and the percentage decreased only slightly to 32% by 1985 (US HHS 2001). If case mothers were less likely to accurately report smoking habits, and if smoking during the year before pregnancy is a true risk factor for childhood cancer, then this could have limited our ability to adjust for the effects of smoking in our results.

Similarly, it's possible that parents of cases were more likely to report the use of bottled water if they perceived of this to be a healthier choice. Or, it's possible that case parents are more likely to remember using bottled water just as they are more likely to remember other details of their past as they tend to reflect on previous habits and details more so than controls parents. Bottled water was reported as the primary drinking water source by 39% of case mothers, but only 20% of control mothers. Again, this information could be accurate, but if reporting bias influenced the reliability of bottled water usage, then adjustment of this factor could bias the results towards the null. A large-scale survey of bottled water usage among pregnant women during the relevant time period was not found. However, other case-control studies involving maternal drinking water exposures during the 1990s tend to report rates of bottled water usage more similar to the controls than the cases in this study. Shimokura et al. (1998) studied well-educated, predominantly white, pregnant women in North Carolina in 1994 and 1995 and reported that 24% primarily drank bottled water at home. Among

a population of lower-income, predominantly white, pregnant women in Colorado during 1996-1997, rates of bottled water consumption were lower (14%) (Zender et al. 2001).

Bottled water usage during the maternal exposure period was adjusted for in two different ways. Assigning zero exposure to those reporting their primary water intake to be from bottled water resulted in a very large number of participants (both cases and controls) being assigned zero exposure, and effect estimates from accompanying regression models were found to be very much attenuated. However, when bottled water usage was instead adjusted for by reducing, but not eliminating, the overall magnitude of estimated contaminant concentrations, ORs for associations between potential maternal NDMA exposure and childhood cancer were consistently elevated. The latter adjustment for bottled water usage likely results in a more plausible exposure scenario considering the likelihood that those reporting use of bottled water as their primary drinking water source undoubtedly experienced some exposure to the estimated concentrations of NDMA in their water either through occasional drinking of tap water, through cooking, or via inhalation during bathing or showering. Adjustment for bottled water intake had less apparent impacts on effect estimates for maternal TCE concentrations and childhood cancer.

A related type of information bias occurs when public awareness of the purpose of a study by participants affects their recall and also their willingness to participate in a study. Some studies have found that participants who agree with a study's known hypothesis may, knowingly or unknowingly, more selectively recall information that supports the hypothesis. This could result in either differential or non-differential bias. More common is the potential for controls to not participate at the same rate as cases because they may be less motivated. As discussed earlier, cases and controls shared similar demographic characteristics, so this bias appears to be an unlikely factor in this study.

CONFOUNDING

As described, we identified a number of childhood cancer risk factors that were plausibly associated with the outcomes in this study and had a p <0.20 with either all cancers or leukemia/lymphoma. Their impact as confounders was assessed for associations between NDMA and TCE and childhood cancer. Sample size limitations precluded full confounding assessment of TCE exposure in the Leukemia/Lymphoma subgroup analyses and limited the confounding assessment to the dichotomous (ever/never) TCE exposure metric.

It was determined that eight variables were acting as confounders of the association between categorical maternal NDMA concentrations and the odds of childhood cancer (i.e. changing the effect estimate of NDMA on cancer by at least 10%). Three of these variables were logically combined into a composite adverse birth event variable, which reduced the number of confounders to be included in a multivariate model to 5. Due to our small sample size, however, inclusion of all confounders in one model produced wildly unstable effect estimates. In trying to reduce the model, it was determined that there was no clear empirical choice for which variables to leave in and which to remove. Therefore, we chose to present results from models of NDMA and one additional covariate in order to give readers an understanding of the impact of each variable. After reviewing all model results, our conclusions regarding the association between NDMA and childhood cancer in this population were not changed. The direction of effect was consistently that of a positive association between maternal NDMA exposure and childhood cancer; this was particularly true of the high exposure group.

Four variables were found to be confounders of the association between estimated ever/never exposure to TCE and childhood cancer. Nevertheless, adjusted models continued to result in positive associations and the conclusion regarding a possible association between TCE exposure and childhood cancer is not changed as a result of risk factor adjustment.

JOINT EXPOSURE TO NDMA AND TCE

Positive associations between childhood cancer and estimated concentrations of drinking water contaminants were observed for both NDMA and TCE, although results for NDMA were more robust. Limitations in the ability to model historical TCE concentrations resulted in a smaller sample size for those analyses, possibly contributing to the lack of statistically significant results. Sub-analysis of TCE concentrations and odds of leukemia/lymphoma cases only was also limited to a dichotomous (ever/never) exposure metric.

When joint exposures were evaluated, it was observed that 31% of cases and 25% of controls were estimated to have been exposed to both contaminants (among the 73 participants with modeled concentrations of both NDMA and TCE) and that a small, but statistically significant, correlation exists between the two contaminants in residential drinking water in this study. Assessing the effects of each contaminant in a multivariate model, while not wholly appropriate due to their correlated nature, nevertheless resulted in continued positive associations with childhood cancer for both the All Cancers group and the Leukemia/Lymphoma subgroup. Such results may suggest independent associations of each contaminant with childhood cancer in this population;

however, the lack of a sample only exposed to TCE and the very small number of those only exposed to NDMA severely limits the ability to evaluate independent effects.

OTHER RISK FACTORS FOR CHILDHOOD CANCER

The primary goal of this study was to assess the risk of childhood cancer from exposure to NDMA or TCE in drinking water. However, numerous other possible risk factors were also evaluated. Particular emphasis was placed on identifying factors associated with cancer risk in this population so that we could control for their effect in estimates of cancer risk from drinking water contaminant exposures.

Although the study targeted a number of possible risk factors for childhood cancer, little is known about what the risk factors for childhood cancer actually are. Scientific research has so far identified known or suspected familial/genetic risk factors that might explain only 5% to 10% of childhood cancers. Those estimates are similar to those for known or suspected environmental risk factors for childhood cancers. Therefore, the cause of 75% to 90% of childhood cancers is still considered unknown (WHO 2008).

Based upon findings reported in the scientific literature (Roman et al. 2018) regarding possible childhood cancer risk factors, we evaluated a large number of variables from environmental exposures to lifestyle behaviors to child and family medical histories. The majority of factors examined showed no association with an increased risk of childhood cancer. However, statistically significant or marginally significant increased risk was estimated for a few factors either in the All Cancer group, the Leukemia/Lymphoma subgroup, or in both groups.

Maternal Medical and Pregnancy History

The risk of childhood cancer and pregnancy factors has often been studied. However, findings on those factors, maternal age at delivery, birth weight, maternal alcohol use, and maternal and paternal smoking during pregnancy, have not always been shown to demonstrate consistent results on the risk with childhood cancer. High birth weight has often been associated with increased risk of acute lymphocytic leukemia (Ross 2006; Charalambous and Vasileiou 2012), which has led some researchers to believe that leukemia originates *in utero* (Hjalgrim et al. 2004). Some studies have shown increased risk associated with maternal smoking and leukemia (MacArthur et al. 2008), but others have not (Pang et al. 2003). Johnson, using data from several state cancer registries, found that the risk of childhood cancer increased with increasing maternal age (2009). However, other studies have shown the opposite (i.e., risk increased with younger maternal age) (Bhattacharya et al. 2014; Schuz et al. 1999).

Further, the findings of increased risk are often only seen with specific types of childhood cancer and not for all childhood cancers (WHO 2008). It is likely that some of these pregnancy factors may not be direct causal factors for childhood cancer but indicators of the processes and stresses of pregnancy on the developing fetus (Schuz et al. 1999; Bhattacharya et al. 2014). Increased risk of high birth weight, for example, may reflect risk associated with higher levels of growth factors, while low birth weight may reflect risks associated with premature development (Roman et al. 2018; Reynolds et al. 2004). Therefore, an explanation for the apparent inconsistent effect of pregnancy factors on childhood cancer likely relates to effects that are very specific and to the fact that studies of childhood cancer often have a small sample size that may limit the study's ability to detect small or moderate levels of risk, especially if the number of cases is insufficient to estimate risk by specific types of childhood cancer (Linet 2003).

The Wilmington study found an elevated statistically significant risk for children with low birth weight and development of childhood cancer. However, this finding is not consistent with what has been generally observed in other studies (Ross, 2006). Since leukemia cases represent the largest cancer group in the Wilmington study, we would have expected a stronger relationship with high birth weight, especially given that low birth weight has usually only been associated with liver cancer (Spector et al. 2009) and only one child with liver cancer was in the study.

Neither maternal smoking, second-hand smoke, nor maternal alcohol consumption during pregnancy, were found to have an elevated odds of childhood cancer (paternal smoking information is included as part of the second-hand smoke variable). While reporting bias may have partially influenced these results, they are consistent with many published studies where it generally appears that second-hand smoke exposure to a child after birth may be a more important risk factor for childhood cancer than smoking during pregnancy (Bhattacharya et al. 2014), although some studies have suggested maternal smoking may increase the risk of some specific types of cancer (Mucci et al. 2004; Schuz et al. 1999).

Infections experienced by a mother and medications received during pregnancy were aspects of a mother's medical history evaluated in the study. Exposure to infectious agents during pregnancy has been the focus of some childhood leukemia research (Belson et al. 2007). Less research has focused on the role of infectious agents and other types of childhood cancer (Alibek et al. 2013). It is known that viruses like cytomegalovirus (CMV), Epstein Barr Virus (EBV), and herpes simplex virus (HSV) can cross the placenta. The possible role of maternal virus infections was assessed in this study population by estimating risk of leukemia/lymphoma and of all cancers as a group. No associations with maternal viral infections and cancer risk were observed in

either group. This is consistent with most other research on the role of infectious agents (Roman et al. 2018).

No statistically significant associations between mother's use of various medications and cancer risk were observed.

Use of two drugs with stronger evidence in the scientific literature of an association with increased risk of childhood cancer—fertility-boosting drugs (Hargreave et al. 2013) and the formerly available DES (thought to prevent miscarriages)—were also evaluated. No case mothers used either of these drugs (3 control mothers used fertility drugs).

Ionizing radiation is a known environmental risk factor for childhood cancer, with a strong relationship with acute leukemias. Most of this evidence comes from studies of atomic bomb survivors and the Chernobyl accident (Belson et al. 2007). However, a significant amount of research has been done to assess the risk of x-ray exposure during pregnancy. This work has led to inconsistent findings, with more recent studies not demonstrating an increased cancer risk, possibly due to reduced radiation dosage (Russ 2007; Shu et al. 2002). Our study results were consistent with these more recent studies in that no case mothers reported x-ray exposure during pregnancy (8 control mothers reported x-ray exposure).

Household Exposures

Household exposure was assessed by evaluating exposure to the child directly or through second-hand exposure when the mother, father, or someone else in the household used the substance in question. Some studies have demonstrated that exposure can occur if exposure is brought into the home on a household member's clothing from an occupational setting (Feychting et al. 2001).

Exposures related to household products (e.g. chemical solvents, pesticides) or activities were also evaluated. A number of exposures were found to have an increased cancer risk, but none of the findings were statistically significant. Household use of plastics, synthetics, or resins was marginally significantly related to childhood leukemia/lymphoma, but as previously noted, reporting bias can't be ruled out. These results may be due to chance due to the small number of study participants and evaluation of multiple comparisons.

Our finding of an increased risk for leukemia/lymphoma from potential household exposures to herbicides, though not statistically significant (p=0.12), has been seen in other studies looking at pesticide exposure. Most of these studies have considered

extensive exposure such as indoor spraying for pests and agricultural spraying. However associations have been consistently seen for leukemia, lymphoma, and brain cancer (Bagazgoitia et al. 2018; Chen et al. 2015; Infante-Rivard and Weichenthal 2007; Zahm and Ward 1998). Davis and others (1993) evaluated the risk of brain cancer from household pesticide use and reported statistically significant associations between use of home pest products and brain cancer in children. Associations have also been seen with leukemia (Bailey et al., 2015; Leiss and Savitz 1995).

Child Medical History

In this study, postnatal supplemental oxygen was found to be associated with risk of childhood cancer. Previous studies have found an association between postnatal supplemental oxygen and risk of childhood leukemia. One such study found an OR of 2.9 (95%CI: 1.2-6.8) among those who were given oxygen by mask immediately after birth (Naumburg et al. 2002). Another found, however, when the data were analyzed for only those children diagnosed with leukemia or lymphoma, the resulting OR was lower and was not statistically significant (OR = 4.8; 95%CI: 0.6-36). The study showing a higher OR is not consistent with other such studies.

CONCLUSIONS

Despite a number of limitations including a small sample size, an exposure assessment based on limited historical data of NDMA and TCE in the town's drinking water, and an inability to account for dietary NDMA exposure, the study was able to reach several important conclusions:

1. Comprehensive information on NDMA in groundwater and the historical Wilmington water distribution system enabled development of a model to predict the movement of NDMA to public water supply wells and in the water distribution system, enabling estimation of monthly NDMA concentrations at each study participant's residence between 1974 and 2000;
2. Detailed interviews of each participant and matched control provided information on major risk factors known or suspected from the published scientific literature for the childhood cancers diagnosed among the Wilmington children;
3. An association between maternal exposure to NDMA during the year before the child's birth and risk of that child developing cancer was strongly suggested by the results of this study. This association was statistically significant for leukemia/lymphoma, marginally significant for all cancers, and a dose-response effect was observed. We cannot rule out that this finding was confounded by exposure to TCE, but the effect is plausibly supported by the literature and could be a real one;
4. A positive association between maternal exposure to TCE during the year before the child's birth and risk of that child developing cancer was not statistically significant and a dose-response effect was not observed, meaning that we cannot rule out the possibility that the finding is due to chance, although it must also be recognized that the study was necessarily underpowered due to a small population and that the association is plausibly supported by the literature. It should also be noted that it is impossible to evaluate the effect of TCE alone using the data available;
5. Minimal evidence for an association between childhood cancer and exposure to NDMA during childhood was observed;
6. A statistically significant increased risk of cancer was observed among a small number of cases who were treated with oxygen immediately following birth, among a small number of cases born with low birth weight, and among cases having any of the adverse birth events reported (oxygen at birth, low birth weight, or incubation).

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