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EXPOSURE TO VOLATILE ORGANIC COMPOUNDS IN DRINKING WATER AND SPECIFIC
BIRTH DEFECTS AND CHILDHOOD CANCERS MCB CAMP LEJEUNE NC
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AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

**Exposure to Volatile Organic Compounds in
Drinking Water and Specific Birth Defects and Childhood
Cancers**

**United States Marine Corps Base
Camp Lejeune, North Carolina**

Study Protocol

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PROJECT OVERVIEW

Title

Exposure to Volatile Organic Compounds in Drink Watering and Specific Birth Defects and Childhood Cancers: United States Marine Corps Base Camp Lejeune, North Carolina

Protocol Summary

Both Camp Lejeune and ABC One-Hour Cleaners were listed as United States Environmental Protection Agency (US EPA) Superfund sites in 1989. The public health assessment for Camp Lejeune determined that exposures to the levels of drinking water contaminants from the dry cleaning establishment and the on-base sources would most likely not result in adverse health effects to adults (ATSDR 1997). However, because of the limited information available in the scientific literature on how these chemicals might affect a fetus or child, it was suggested that an epidemiological study be performed at Camp Lejeune to evaluate whether mothers exposed during pregnancy to chlorinated solvents (e.g., PCE and TCE) in drinking water had a higher risk of giving birth to a child with a birth defect or a childhood cancer.

The Agency for Toxic Substances and Disease Registry (ATSDR) conducted a study to determine if small for gestational age (SGA) was associated with exposures to TCE and PCE in drinking water supplies at Camp Lejeune (ATSDR 1998; Sonnenfeld et al. 2001). The study showed that exposure to Hadnot Point water was associated with an elevated risk for SGA (OR=3.9, 90% CI: 1.1, 11.9) only among male infants (ATSDR 1998). Exposure to Tarawa Terrace water was associated with elevated risk for SGA among infants born to mothers aged >35 years (OR=2.1, 90% CI: 0.9, 4.9) and among mothers with two or more prior fetal losses (OR=2.5, 90% CI: 1.5, 4.3) (Sonnenfeld et al. 2001).

ATSDR has conducted a health survey of the population who were conceived or carried in utero while their mothers lived in on-base housing at Camp Lejeune during 1968-1985 (ATSDR 2003). The objective of this health survey was to identify and confirm all reported cases of specific birth defects and childhood cancers among children exposed in utero to drinking water contaminated with TCE, PCE, and other chlorinated solvents at Camp Lejeune during the study period.

Based on the recommendation for an epidemiological study, the health survey results, and scientific literature, ATSDR decided to further investigate the relationship between exposure to contaminated drinking water and childhood cancer including leukemia, as well as specific birth defects including spina bifida, anencephaly, cleft lip and cleft palate via a case-control study.

In the current protocol, verified and potential cases (identified in the health survey) and a random sample of non-cases will be selected for inclusion in a case-control study assessing the relationship between exposure to contaminated drinking water and the incidence of childhood cancer and specific birth defects in this population. Detailed interviews will be administered to parents or the offspring in order to obtain data on maternal water consumption habits, residential history, and on maternal and paternal risk factors.

Investigators & Roles/Funding Sources

The Principal Investigators will include Frank Bove, ~~James Tsai~~, Perri Zeitz Ruckart, and Shannon Rossiter. The project will be supervised by Dr. Wendy Kaye. All are epidemiologists within the Division of Health Studies at ATSDR. ~~XXXXX~~ Westat (Contract #200-2004-10319) was selected as the contractor to interview both cases and controls. Funding is being provided by ~~XXXXXX~~ DOD.

INTRODUCTION

Literature Review/Current State of Knowledge About VOCS in Drinking Water

The Agency for Toxic Substances and Disease Registry (ATSDR) is required by law to conduct a public health assessment at each of the sites on the National Priority List (NPL). The aim of each assessment is to determine whether the population residing around a particular site might have been exposed to any toxic substance and also to assess whether there might have been any adverse health effects resulting from this exposure. Known health effects are documented in these assessments and public health recommendations are made accordingly. Potential health effects are also identified and referred to ATSDR scientists for additional investigation.

As part of this health assessment process, mixtures of volatile organic compounds (VOCs) containing high levels of trichloroethylene (TCE) and tetrachloroethylene (PCE) were documented in two drinking water supplies at Camp Lejeune over a period of 34 months. The population that was supplied with this water was slightly more than half of all residents in family base housing. Because this population consisted of a large proportion of young married women, concern was raised about potential health effects on fetuses exposed to toxic substances in utero.

U.S. Marine Corps (USMC) Base Camp Lejeune covers an area of approximately 233 square miles in the City of Jacksonville, North Carolina. Base housing for enlisted personnel, officers, and their families were located in 15 different areas on the base. Based on Camp Lejeune family housing records, we estimate that at least 180,000 people were potentially exposed to VOCs while living in family housing during 1968-1985. This estimate is derived from information that almost 90,000 military members were assigned to family housing during this time period (ATSDR 1998), and family housing was assigned to military members with two or more people in their household. To meet the water needs of a base this size, an average of 8.3 million gallons of water was distributed daily. To do this, more than 100 wells had been drilled. Almost all of these wells used a sand aquifer which is permeable to contamination (Weston, Inc 1992).

In 1982, groundwater contamination was detected in wells that fed the family base-housing areas on

Camp Lejeune. This coincided with a change in the laboratory method and was unlikely to be the onset of contamination. Because there were no water quality standards for the detected VOCs in 1982, and the source of the contamination was not identified, no action was taken until approximately 2 years later.

In July 1984, Camp Lejeune began sampling wells in the Hadnot Point area as part of the base Superfund program. Contaminated wells were closed soon after they were identified in January and February 1985, and a routine sampling program was implemented at all distribution systems on the base. Notable contamination has not been detected in Camp Lejeune's drinking water systems since February 1985.

There were several sources of contamination. The on-base sources included: (a) leaking underground storage tanks containing trichloroethylene (TCE), (b) spills from operations at the vehicle maintenance area, and (c) drum disposal at sites 6, 9, and 82 and associated storage lots at operating unit 2 (ATSDR 1997). The off-base source consisted of a leaking, above-ground, tetrachloroethylene (PCE) storage tank and solvent disposal practices at ABC One-Hour Cleaners, a dry cleaning establishment (ATSDR 1990).

Three water distribution systems provided water for Camp Lejeune's family base housing areas: the Tarawa Terrace, Holcomb Boulevard, and Hadnot Point systems. Because it was not known when the contamination started in each of the distribution systems, chemicals could have been present in the systems for many years before their initial discovery in 1982.

- I **Tarawa Terrace.** Contamination at this water system occurred as a result of disposal practices at ABC Cleaners, which opened in 1954 and was located off-base just outside the gate from Camp Lejeune. The establishment disposed waste solvent in their septic tank system and the ground. In 1958, a drinking water supply well was drilled on-base by the Marine Corps. This well was located 900 feet from the dry cleaners. It is likely that this well was contaminated soon after it was drilled because of its proximity to the source of contamination and the high permeability of soils in the area (ATSDR 1998). Sampling of the finished water at the Tarawa Terrace system began in 1982, and high levels of PCE

were found (76 ppb – 104 ppb); this range is based on four samples collected during May-July 1982 with a mean of 85.5 ppb. PCE is a dry cleaning solvent. In the one sample taken in 1985 before the contaminated wells were shut down, a PCE level of 215 parts per billion was found. In addition, TCE, a degreaser, and 1,2-dichloroethylene (DCE), a breakdown product of PCE were also detected in this sample. The contaminated wells were closed in February 1985 (ATSDR 1997).

! **Hadnot Point.** This water distribution system supplied water primarily for industrial purposes at the base but it also supplied drinking water to the Hospital Point housing area. High levels of TCE (a maximum of 1,400 ppb) were detected during sampling in 1982. High levels of TCE and DCE were found during the routine testing of the drinking water system in 1984 and 1985. The Hadnot Point system has 39 operational wells, although only approximately 20 wells were used at any one time. The contamination was linked to leaking on-base underground storage tanks.

[**Holcomb Boulevard.** In 1972, the Holcomb Boulevard system went on-line and served the Midway Park, Berkeley Manor, Watkins Village, and Paradise Point areas of base housing. Before 1972, the Holcomb area was served by the Hadnot Point water distribution system. In early 1985, a fuel line accidentally burst at the Holcomb Boulevard water distribution system, releasing fuel into the water supply. To remediate the problem, the Holcomb water supply was provided by an emergency line from the Hadnot Point system. The emergency hookup occurred over a 12-day period starting on January 27, 1985. During this period, the Holcomb area base housing received contaminated water from the Hadnot Point system. Once the fuel line was repaired, the emergency hookup from Hadnot Point was disconnected, and the Holcomb Boulevard system resumed service to its designated housing areas.

Each of the affected housing areas received water containing a mixture of several contaminants, a phenomenon noted with almost every population exposed to contaminants released from hazardous

waste sites.

ATSDR's 1997 public health assessment (PHA) for Camp Lejeune found that PCE was the primary contaminant at ABC One-Hour Cleaners (ATSDR 1997). PCE and other solvents from the dry cleaning establishment had contaminated a nearby well on Camp Lejeune property that provided drinking water to the Tarawa Terrace family base housing.

This PHA also determined that exposures to the levels of drinking water contaminants from the dry cleaning establishment and the on-base sources would most likely not result in adverse health effects to adults (ATSDR 1997). However, because of the limited information available in the scientific literature on how these chemicals might affect a fetus or child, it was suggested that an epidemiological study be performed at Camp Lejeune to evaluate whether mothers exposed during pregnancy to chlorinated solvents (e.g., PCE and TCE) in drinking water had a higher risk of giving birth to a child with a birth defect or a childhood cancer.

As a first response to this recommendation, ATSDR conducted a study to determine if having a SGA infant at Camp Lejeune was associated with exposures to water supplies from Tarawa Terrace contaminated with PCE and water supplies from Hadnot Point contaminated with TCE and 1,2-dichloroethylene (ATSDR 1998; Sonnenfeld et al. 2001). Exposure to Hadnot Point water was associated with an elevated risk for SGA only among male infants (OR=3.9, 90% CI: 1.1, 11.9) (ATSDR 1998). Exposures to Tarawa Terrace water was associated with elevated risk for SGA among infants born to mothers aged ≥ 35 years (OR=2.1, 90% CI: 0.9, 4.9) and among mothers with two or more prior fetal losses (OR=2.5, 90% CI: 1.5, 4.3) (Sonnenfeld et al. 2001).

An important feature of the exposure at Camp Lejeune was its intermittent nature. Each of the contaminated systems had more wells than were necessary to supply water on any given day. Contaminant levels have been noted to vary with the supply wells in service. The process by which a particular well was selected for use on any given day was essentially random, but the Camp Lejeune PHA (ATSDR 1997) and the previously conducted study of SGA among births at Camp Lejeune (Sonnenfeld et al. 2001) assumed that all wells were in use in any given month

unless they were taken out of service for mechanical failure or contamination. Daily or monthly well usage logs were not available for the PHA or the SGA study to evaluate this assumption. The current study will evaluate this assumption by obtaining additional information on the distribution system and by conducting extensive distribution system simulation models and sensitivity analyses.

Toxicology of PCE and TCE

Previous experience with environmental and pharmacologic agents has shown that human gestation is a time of great vulnerability; the developing fetus is sensitive to various chemical insults. The chemical contaminants in the water, PCE and TCE, are structurally similar chemicals with many common toxicological properties. Both compounds are lipophilic (ATSDR 1997) and readily cross the placenta (Laham 1970; Ghantous et al. 1986; Fisher et al. 1989; Goldberg et al. 1990). TCE and PCE are organic solvents that can be absorbed orally, by inhalation, or by dermal contact. PCE is a colorless organic compound that has been used as an industrial solvent for over 50 years and as a dry cleaning agent for over 30 years (Doyle et al. 1997). Compared with other solvents, both TCE and PCE have relatively long half-lives in the human body; in the blood, these half-lives are approximately 70-100 hours and 4-8 days, respectively (Ikeda et al. 1977). A number of models have been developed to estimate the distribution of PCE and TCE within the human body following exposure to contaminated air or groundwater (Rao et al. 1993; McKone et al. 1992; Allen 1993).

Although ingesting contaminated drinking water is an efficient way to deliver these toxic chemicals to the fetus, inhalation of TCE and PCE that have evaporated from the drinking water is likely to result in higher exposures than ingestion. Activities such as bathing, showering, cooking, and operating washing machines and dishwashers cause VOCs in drinking water to evaporate (McKone 1987).

A larger fraction of PCE and TCE are metabolized following ingestion than inhalation. Moreover, trichloroacetic acid (TCA), a biologically active metabolite of PCE and TCE, has been observed to persist in the rat fetus after exposure to either PCE or TCE has stopped. Therefore, the relative contributions of inhalation and ingestion of PCE and TCE to toxicity depend on whether or not the primary toxic actor is the chemical itself (i.e., PCE or TCE) or a chemical metabolite such as TCA.

The International Agency for Research on Cancer (IARC) has classified TCE and PCE as probably carcinogenic to humans; this classification was based on limited evidence in human studies and sufficient evidence in animal studies (IARC 1995). In 2002, the Tenth Annual Report on Carcinogens of the National Toxicology Program (NTP) determined that TCE was “reasonably anticipated to be a human carcinogen”; this determination was based on limited evidence from human studies, supporting evidence from animal studies, and convincing evidence that TCE acts through mechanisms relevant to carcinogenesis in humans (NTP 2002). This report also stated, on the basis of findings of animal studies, that PCE was “reasonably anticipated to be a human carcinogen.” In a draft health risk assessment released in August 2001, EPA concluded that TCE was “highly likely to produce cancer in humans”; this conclusion was based on a review of the occupational epidemiology literature and animal data that supported the findings from the occupational studies (NTP 2001). IARC and NTP have not determined a cancer classification for cis-1,2-dichloroethylene or trans-1,2-dichloroethylene.

Although useful in generating hypotheses regarding the developmental hazards of specific contaminants, toxicological studies are complicated by the need to extrapolate from animal species and high doses. In addition, laboratory studies do not adequately capture the complex personal and environmental context in which human exposures to VOCs occur (Hertz-Picciotto 1995). For these reasons, the findings of the limited epidemiological studies are emphasized.

Literature Review of VOC-Contaminated Drinking Water and Birth Defects and Childhood Cancers

The current study will build upon findings of previous studies and add to the current body of knowledge. The decision to focus on childhood leukemia, spina bifida, anencephaly, cleft lip, and cleft palate in the current study was based on the evidence from the scientific literature as well as the ability of the 1999-2002 ATSDR survey (from which the study population will be drawn) to identify reliably and completely all the cases of these diseases (ATSDR 2003). The current study originally planned to include childhood non-Hodgkin's lymphoma, however the survey was not able to adequately confirm a sufficient number of cases to further study this outcome. No more than four potential case of non-Hodgkin's

lymphoma were identified. Although the current study will not include a large number of cases, Camp Lejeune provides a good opportunity to study the outcomes of interest because the exposure data can be well characterized.

Inclusion of the cited studies in the literature review was based on the following criteria: strength of association including the magnitude of the measures of effect and the precision of the estimates; exposure-response trends; and biologic plausibility.

Birth Defects

Birth defects are the leading cause of infant mortality in the United States and may be responsible for more than 20% of all infant deaths (Wang et al. 2002). In the United States, nearly 150,000 babies are born with a birth defect each year (March of Dimes 2003). It has been reported that 1 in 800 births will have a cleft lip or a cleft palate and about 6 per 10,000 births will have a neural tube defect (anencephaly or spina bifida).

VOC-Contaminated Drinking Water and Birth Defects

Three studies have evaluated associations between exposures to drinking water contaminated with TCE, PCE, and other chlorinated solvents and birth defects (Bove et al. 2002). One study was conducted in Tucson, Arizona, where a public drinking water well was contaminated with TCE at a maximum level of 239 ppb (Goldberg et al. 1990). A case-control study of heart defects found an increased risk associated with exposure to the contaminated public well. A prevalence ratio of 2.6 (95% CI: 2.0, 3.4) could be calculated based on information provided in the article (Bove et al. 2002).

A study of 75 towns in northern New Jersey evaluated the following birth defect groups: all central nervous system (CNS) defects, neural tube defects (NTDs), oral clefts, and major structural heart defects. Elevated risks for CNS (OR=1.7, 90% CI: 0.8, 3.5) and NTD (OR=2.5, 90% CI: 0.9, 6.4) were found at TCE levels above 10 ppb. In addition, elevated risks for oral clefts (OR=2.2, 90% CI: 1.2, 4.2) were found at TCE levels above 5 ppb (Bove et al. 1995). The risk for oral clefts was elevated for PCE levels above 10 ppb (OR=3.5, 90% CI: 1.3, 8.8). Because 1,1-dichloroethylene and 1,2-dichloroethylene were detected very infrequently and usually at levels < 5 ppb in the drinking water supplies in northern New Jersey, the study

evaluated total dichloroethylenes. Elevated risks for CNS (OR=2.5, 90% CI: 1.2, 5.1), NTD (OR=2.6, 90% CI: 0.9, 6.5), and oral clefts (OR=1.7, 90% CI: 0.6, 4.2) were found at total dichloroethylene levels > 2 ppb.

A study at Woburn, Massachusetts, evaluated associations between exposure to the contaminated drinking water from public wells G and H and birth defects (Massachusetts Department of Public Health et al. 1996). A recent review of drinking water studies (Bove et al. 2002) presented odds ratios that were calculated based on information provided in the Woburn study report. Elevated risks were found for eye defects (OR=4.4, 95% CI: 0.5, 39.6), NTD (OR=2.2, 95% CI: 0.2, 24.4), and cleft lip (OR=2.2, 95% CI: 0.2, 24.4). The elevations in risk for NTD and cleft lip were based on 2 exposed cases, and there were no exposed cases of cleft palate.

In summary, the literature on the association between birth defects and maternal exposure to drinking water contaminated with organic solvents such as TCE and PCE is limited. Nevertheless, the findings of excess NTDs and clefts in the northern NJ and Woburn studies are suggestive of an effect and should be studied further. The current study will be an important contribution to the scientific literature on the adverse health effects of exposures to these contaminants in drinking water.

Occupational Exposures to Solvents and Birth Defects

Several studies have examined the issue of pregnancy outcomes and occupations where women may have been exposed to VOCs. Unfortunately, only a small number of these studies have examined exposure to specific chemicals or chemical classes. Further limitations to many occupational studies include indirect assignment of exposure based on job title rather than measuring occupational exposure. Additionally, because exposure to many different substances occurs in the same work place, the relevant hazards could be difficult to identify (Sieber et al. 1991).

A small case control study of birth outcomes among female workers in Sweden, Finland, and Norway found no association between congenital malformations and working in the dry-cleaning or laundry industry (Olson et al. 1990). In addition to the limitation of having a very small study (26 cases), these authors grouped congenital malformations, low birth weight, and stillbirth into one outcome or case definition. This categorization ignored the different times at which developing organisms are vulnerable to still birth or

low birth weight as compared to when they are vulnerable to congenital malformations.

A case-control study investigated whether occupational and hobby chemical exposures to women in the periconceptional period increased their risk for having pregnancies affected by NTDs (Shaw et al. 1999). An industrial hygienist assigned exposure categories a priori to each occupational task and hobby. Exposure categories included 74 chemical groups, 9 end-use chemical groups, and organic solvents. These authors concluded that maternal exposure to a variety of chemicals in the periconceptional period did not contribute to risk of NTDs. One limitation to this study is the a priori assignment of exposure categories that may have not accurately reflected their true exposure.

A prospective, observational study looked at 125 pregnant women who were occupationally exposed to organic solvents during their first trimester of pregnancy (Khattaak et al. 1999). Significantly more malformations occurred among fetuses of women exposed to organic solvents than controls (RR= 13.0, 95% CI: 1.8-99.5). The authors concluded that this risk appeared to be increased among those women who reported symptoms associated with their exposure.

Environmental exposures differ from those in the occupational setting in a number of ways. Environmental exposures often occur through contaminated drinking water whereas occupational exposures usually occur through inhalation or skin contact. Occupational exposures also tend to be at a higher concentration than environmental exposures. Furthermore, environmental exposures are not limited to a 40-hour work week, and can occur in populations that may not be present in the work force. These factors may limit generalizations between occupational and environmental settings of toxic exposures.

Other Risk Factors for Birth Defects

Risk factors for birth defects include family history as well as maternal risk factors such as diabetes, fevers during pregnancy, medication use during pregnancy, age, socioeconomic status, education, smoking during pregnancy, occupation, and diet (Table 1) (Wang et al. 2002; Hernandez-Diaz et al. 2001; Ritz et al. 2001; Rasmussen et al. 2001; Loffredo 2000). Smoking during pregnancy has been associated with an increased risk for birth defects including oral cleft defects.

It is widely accepted that folic acid supplementation reduces the risk of NTDs (Werler et al. 1999).

Data indicate that exposure to folic acid antagonists during first or second month after the last menstrual period more than doubled the risk of NTDs (Hernandez-Diaz et al. 2001). Reports have suggested that multivitamin supplementation before or early in pregnancy reduces the risk of NTDs and other specific malformations in the lip and palate, heart, limbs, urinary tract, brain, and pylorus muscle (Werler et al. 1999).

Recent studies have suggested that maternal obesity may increase the risk of NTDs in infants and fetuses (Li et al. 1996). This association does not appear to be mediated by folate intake; an estimated threefold increase in risk was estimated in the heaviest group of women independent of folate intake (Li et al. 1996).

Childhood Leukemia

Past epidemiologic studies have relied on International Classification of Disease (ICD) in the categories of acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). The classification underlines the differences in disease symptom, diagnosis, treatment, prognosis, and etiology. ALL is most common in children, about 85% of cases of ALL occur in children, and 90% of leukemia that occurs in children is ALL (Myers 1990). ALL is highly curable now and it responds well to chemotherapeutic treatments. CLL is pre-dominantly a disease of the elderly; it progresses slowly and is not curable. CLL is considered an entity of Non-Hodgkin's lymphoma (NHL). AML and CML are common in adults and incidence increases with age (Cancer Epidemiology 2002).

ALL is the most common type of leukemia; it is also the most common type of cancer in children. Leukemia of all types accounts for approximately one-third of all pediatric malignancies (Ries 1999). Leukemia comprises a heterogeneous group of acute and chronic lymphocytic and myelogenous malignancies originating in different cells of the hematopoietic system. The age incidence of leukemia is bimodal, with an early peak incidence between ages 2 and 4 years, and a second one at around 25 (Reynolds 2002; Cancer Epidemiology 2002). Incidence rates are usually higher in males than in females, and higher among whites than among blacks (Parkin 1992).

VOC-Contaminated Drinking Water and Childhood Leukemia

Past epidemiologic studies have been conducted to evaluate the associations between childhood

cancers and exposures to drinking water contaminated with TCE and/or PCE. A study conducted in 75 towns in northern New Jersey found an association between drinking water contaminated with TCE above its maximum contaminant level (MCL) of 5 ppb and ALL among females only (Cohn 1994). For females diagnosed with ALL before their 5th birthdays, the rate ratio was 4.5 (95% CI: 1.5, 10.6). A recently published study found that exposure to the contaminated drinking water was associated with childhood leukemia in Woburn, Massachusetts (Costas 2002). Drinking water from public wells G and H were contaminated primarily with TCE (267 ppb) but also contained much lower concentrations (<25 ppb) of PCE and trans-1,2-dichloroethylene. The association was highest for in utero exposures (RR=8.3, 95% CI: 0.7, 94.7). A study conducted in Toms River, New Jersey, found an association between drinking water contaminated with TCE, PCE, and a styrene-acrylonitrile trimer and childhood leukemia among females only (New Jersey Department of Health and Senior Services 2003). The association was highest for in utero exposures (OR=5.0, 95% CI: 0.8, 31.0).

Other Risk Factors for Childhood Leukemia

There have been a number studies on the causes of leukemia (Table 1) Leukemia cases have been linked to intrauterine exposure to ionizing radiation (Shu 1988). Down's syndrome (Avet-Loiseau 1995; Cnattingius 1995), and certain inherited disorders such as Bloom's syndrome (Yankiwski 2000), Fanconi's anemia, ataxia-telangiectasia (Olsen 2001) are also believed to be associated with childhood leukemia. Parental age and parity has not been found to be related to childhood leukemia risk in most studies. (Little 1999). Occurrence of childhood ALL is high among identical twins. Familial clustering has been reported mostly with adult leukemia, especially CLL and AML (Yuille 2000). There is inconclusive evidence that smoking and alcohol intake increase the risk of any types of leukemia (Severson 1987; Brownson 1989; Shu 1996; Adami 1998). Some evidence is available to link immune deficiency diseases with leukemia (Gatti 1971). Infections such as human T-cell leukemia/lymphoma virus (HTLV) and Epstein-Barr (EBV) may be responsible for a small fraction of the leukemia cases (Cancer Epidemiology 2002). Extreme low-frequency electric and magnetic fields (ELF-EMF) have been studied in brain tumors and various forms of leukemia (Oak Ridge Associated Universities 1992; Linet 1997). However, little evidence is available to link ELF-EMF

to leukemia among adults. The results of childhood leukemia studies indicate the role of ELF-EMF in the etiology is unlikely but not impossible (Linnet 1997; Angelillo 1999). Other less consistently reported findings included the associations of childhood leukemia with previous fetal loss and high birth weight (Reynolds 2002). Prenatal diagnostic x-rays, particularly during the last trimester of pregnancy, have been linked to leukemia ALL (Boice 1981). In addition, the administration of growth hormone (Ross 1996; Petridou 2000) and certain drugs, including cancer chemotherapeutic agents such as cyclophosphamide and melphalan have been linked to secondary leukemia particularly AML (Swerdlow 1992). Other drugs may have been implicated (i.e. chloramphenicol and pregnancy related analgesics), but evidence so far has been inconclusive (Petridou 1997). Furthermore, occupational exposures to pesticides, organic solvents and chemicals including benzene, styrene, TCE, PCE, paint thinners have been suggested as possible risk factors for leukemia in adults (IARC 1987; Delzell 1985; Mueller 1996).

In summary, the results of the above studies have suggested links between TCE, PCE exposure, and leukemia risks. As the result of these study findings, this study will examine the potential impact of exposure to VOCs in drinking water at Camp Lejeune on childhood leukemia, particularly ALL.

Justification for Study

ATSDR was established by Congress in 1980 under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), also known as the Superfund law. This law set up a fund to identify and clean up hazardous waste sites in the United States (U.S.). The U.S. Environmental Protection Agency and the individual states regulate the investigation and cleanup of the sites. Data collection is authorized under Section 104(l) (6) (B) of CERCLA, P.L. 96-510 (Appendix I).

ATSDR has a broadly defined legislative mandate to prevent or mitigate adverse human health effects and diminished quality of life resulting from exposure to hazardous substances in the environment. Population-based research conducted to identify links between exposures and specific adverse health effects is a necessary part of this mandate. One exposure-disease relationship that warrants further exploration is that between VOCs in drinking water and childhood cancer or specific birth defects. These outcomes may be of particular importance to populations residing on military bases because such

populations have a high proportion of individuals of reproductive age.

ATSDR has documented TCE, PCE, and 1,2-dichloroethylene contamination in water systems supplying two different family base housing areas at Camp Lejeune. Each of the affected housing areas received water containing a mixture of contaminants. There are two big differences between this scenario and the typical hazardous waste scenario: (1) there is documentation that these exposures occurred and (2) water sampling data gives us a very good idea what people were exposed to (i.e., what the mixture contained, what the primary constituents of the mixture were, and what the levels of the constituents were, at least at the time of sampling).

In response to the PHA recommendation, ATSDR began the multi-step process of determining the appropriateness of conducting an epidemiological study of specific childhood cancers and birth defects at Camp Lejeune. The first step was to determine which childhood health problems to study. Based on the scientific literature, ATSDR decided to focus on specific childhood cancers and birth defects: childhood leukemia, spina bifida, anencephaly, cleft lip and cleft palate.

The second step was to identify the children eligible for the study by doing a telephone survey. ATSDR decided on children born to women who were pregnant with them while living on the base during 1968–1985. The year 1968 is the starting point because that year North Carolina began computerizing its birth records. These records were used to identify children for the study. The end point is 1985 because the tainted wells were shut down that year.

The survey began in September 1999 and ended in January 2002. ATSDR surveyed by telephone the parents of 12,598 eligible children. This number was about 80% of the estimated total. Parents were asked if the child had had a birth defect or had developed a childhood cancer. A total of 99 cases of childhood leukemia, spina bifida, anencephaly, cleft lip and cleft palate were reported (Appendix II).

The third step was to confirm the children's health problem(s). ATSDR asked the parents who reported that their children had health problems of interest (or the children if they were now over 18) for access to their child's health records. These records are now under review. ATSDR has received records for 60 of the 99 children so far and has confirmed about 80% as being correctly reported.

The final step will be to conduct a case-control study. This study will include all confirmed cases of the birth defects and childhood cancers which are the focus of the study. The study will also include modeling of the water system to see which mothers did and did not receive the water with VOCs. Currently we do not know which mothers received the water with VOCs.

In summary, ATSDR has finished the survey and is now confirming the cases. These steps were needed to prepare for the larger study. There is enough information to proceed with the full study. Only the case-control study can establish whether VOC-tainted drinking water may cause the childhood health problems being studied.

Intended/Potential Use of Study Findings

To date, information regarding the health effects of exposures to drinking water contaminated with TCE and PCE are extremely limited. The findings of this study at Camp Lejeune should further our understanding of the health effects of TCE or PCE exposure from community drinking water and will help us better focus our prevention efforts.

Study Design/Locations

ATSDR will conduct a case-control study of cases of childhood cancer or specific birth defects and a random sample of controls to assess the relationship between VOC exposure and the incidence of childhood cancer and birth defects in children born to parents while residing at Camp Lejeune from 1968 to 1985. Both cases and controls may currently reside anywhere in the United States.

Objectives

The overall objective of this study is to examine the associations between maternal exposures within a 1-year period before child's birth to TCE and PCE in drinking water at Camp Lejeune during the period of 1968-1985 and risk of specific birth defects and childhood leukemia (ALL) in offspring.

Hypotheses

1. a. There is no association between ever drinking TCE/PCE contaminated water during the first trimester and the risk of specific birth defects.

- b. There is no association between ever drinking TCE/PCE contaminated water during each trimester and the risk of leukemia (ALL).
- 2. a. There is no association between exposures to different concentrations of TCE/PCE in drinking water during the first trimester and the risk of developing specific birth defects.
 - b. There is no association between exposures to different concentrations of TCE/PCE in drinking water during each trimester and the risk of leukemia (ALL).
- 3. a. There is no association between exposures during the first trimester to ever/never or to different concentrations of TCE/PCE in drinking water, taking into account the amount of water used (i.e., showering, hand washing dishes) or consumed by the mother, and the risk of specific birth defects.
 - b. There is no association between exposures during each trimester to ever/never or to different concentrations of TCE/PCE in drinking water, taking into account the amount of water used (i.e., showering, hand washing dishes) or consumed by the mother, and the risk of leukemia (ALL).

METHODS

Study Rationale

The association between birth defects and drinking water contaminated with TCE or PCE could not be reasonably evaluated in the 1998 study of "Volatile Organic Compounds in Drinking Water and Adverse Pregnancy Outcomes, United States Marine Corps Base, Camp Lejeune, North Carolina" because of extreme under-ascertainment of cases using data from birth certificates (ATSDR 1998). Scientific literature has suggested that organic solvents such as TCE and PCE may be risk factors for leukemia.

A 1999-2002 ATSDR survey of parents who resided at Camp Lejeune at any time during pregnancy between 1968 and 1985 identified children with birth defects or childhood cancers through parental self-report. ATSDR is in the process of reviewing the medical records for children with specific birth defects and childhood cancers that were identified by the survey. This current protocol proposes to examine the relationship between specific birth defects and childhood cancers and TCE- or PCE-contaminated drinking water by mathematically modeling the mother's exposure to contaminated water

during her pregnancy.

Study Design

ATSDR will conduct a case-control study of cases of childhood cancer or specific birth defects and a random sample of controls to assess the relationship between VOC exposure and the incidence of childhood cancer and birth defects in children born to mothers who resided at Camp Lejeune from 1968 to 1985. Both cases and controls may currently reside anywhere in the United States. A case-control study is the most appropriate study design because specific birth defects and childhood cancers are rare, and extensive exposure information gathering through an approximation technique and parental interview is planned.

Exposure Assessment

In order to provide a quantitative estimate of exposure, spatial and temporal distributions of contaminant-specific compounds are required for the duration of the study (1968–1985). Ideally, tap samples of household water for contaminant-specific compounds would be required for each study subject. Owing to the paucity of historical, contaminant-specific data, this approach is not possible. An alternative approach is to reconstruct estimates of the spatial and temporal distribution of the contaminant-specific compounds at locations (such as residences) serviced by a water-distribution system, including the residence locations of study subjects. Using an approximation technique, such as water-distribution system modeling, can provide the proportional contribution of water from a water source to any location serviced by the water-distribution system. This technique can also provide the relative concentrations of contaminant-specific compounds mixed with the water delivered to study subject residences. Such an approach has been successfully used in two epidemiological studies that have gained national attention.

In Woburn, Massachusetts, water-distribution system modeling was used to provide contaminated public water exposure estimates for subject residences (Murphy 1991; Costas et al. 2002). Specifically, Murphy (1991) developed a water-distribution system model to estimate the distribution of contaminated water potentially delivered to each Woburn residence from contaminated wells G and H. In Dover Township, New Jersey, results of water-distribution modeling were used to develop exposure indexes for

historically contaminated public water supply in a case-control study of childhood cancers (Maslia et al. 2001; NJDHSS 2003). In this analysis, Maslia et al. (2001) applied the concept of proportionate contribution, derived from results of water-distribution system modeling, to estimate the percentage of water delivered to any study location for any source of public water. This analysis reconstructed the monthly distribution of water from January 1962–December 1996.

In applying the estimation method described above (historical reconstruction using water-distribution system modeling) to the proposed case-control study, the following protocol will be used:

- I. Development of a computerized network model of the present-day water distribution system;
 - (a) field-data collection of the present-day system operations; and
 - (b) hydraulic and water-quality calibration and testing of the present-day model based on the field data;
- II. Development of historic distribution system models through the study period, 1968–1985;
 - (a) historical reconstruction of hydraulics within the water-distribution system;
 - (b) historical reconstruction of fate and transport of contaminants within the water-distribution system;
 - (c) comparison of historical contaminant concentrations with measured tap sample data for specified locations and times; and
 - (d) assignment of the monthly contaminant concentrations for historical period for all study locations.

The exposure assessment methods in the current study will most likely estimate concentrations by year and housing complex. However, depending on the completed model, it may be necessary and possible to estimate contaminant levels at different locations within each housing complex.

Study Population

The 1998 ATSDR adverse pregnancy outcomes study at Camp Lejeune obtained birth certificate information on the 12,493 children born to parents known to have been stationed at Camp Lejeune during pregnancy between 1968 and 1985. These years were chosen because 1968 is the first year that birth

certificates were computerized in North Carolina and 1985 is the last year that VOC contamination was detected at the base. This time period also provided a sufficient sample size to conduct the study. An estimated additional 4,000 births occurred elsewhere to personnel who were stationed at Camp Lejeune at some point during pregnancy during the 1968-1985 timeframe (ATSDR 2003). A referral process was used to obtain information on personnel who were pregnant while residing at Camp Lejeune during 1968-1985 but who delivered elsewhere. Additionally, a media campaign was used to find personnel stationed at Camp Lejeune during pregnancy who could not be located as well as the estimated 4,000 births that occurred elsewhere. Names of personnel identified through referral or by the media campaign were cross-referenced with military databases.

A 1999-2002 ATSDR survey located 12,598 children born to parents who resided at Camp Lejeune at any time during pregnancy between 1968 and 1985. Children eligible for the survey were those born at 28 weeks or more gestation to mothers who were pregnant while they lived in base housing at Camp Lejeune during 1968-1985. Survey respondents were asked basic demographic questions as well as if the child was diagnosed with cancer before age 20 or if the child was diagnosed with a birth defect before age 5. If the child had cancer or a birth defect, the type of cancer or birth defect was also collected. Parental reports of cancer and birth defects are being verified by reviewing medical records. If medical records are not available to confirm a case, we will use other appropriate documentation such as the birth certificate, death certificate, or information obtained from a recent doctor's visit (e.g., a dental visit for potential cleft cases or physical therapy records for potential spina bifida cases) (Appendices VI, VII, VIII). The following cases of selected birth defects and cancers have been reported: 35 neural tube defects (NTDs), 42 oral cleft defects, and 22 childhood leukemias. To date, records have been obtained for 20 NTDs (15 confirmed as having NTDs; 5 confirmed as not having NTDs), 1 was ineligible, 1 refused, and 13 are still pending. Records have been obtained for 23 oral cleft defects (20 confirmed as having oral cleft defects; 3 confirmed as not having oral cleft defects), 3 refused, and 16 are still pending. Records have been obtained for 17 childhood leukemias (12 confirmed as having leukemia; 5 confirmed as not having leukemia), 2 were ineligible, and 3 are still pending.

Eligibility (Participant inclusion/exclusion criteria)

Potential cases consist of children with the following birth defects or childhood cancers who were born to mothers who resided at Camp Lejeune during their pregnancies between 1968 and 1985: NTDs (consisting of anencephaly and spina bifida), oral clefts (consisting of cleft lip with and without cleft palate and cleft palate), and childhood leukemias. Familial cases of leukemia, children who were 20 years of age or older when diagnosed with leukemia, or children who were 5 years of age or older when diagnosed with NTDs or oral clefts will be excluded. Only confirmed cases will be included in the primary analyses. We will consider doing a secondary analysis including unconfirmed cases.

Potential controls consist of children without these birth defects or childhood leukemias who were born to mothers who resided at Camp Lejeune during their pregnancies in the same time period and participated in the survey. We will attempt to enroll ten times as many controls as cases. One control group will be utilized for all of the cases of both birth defects and childhood leukemias. Control selection will be performed by using a randomization procedure. The only risk factor that has a skewed distribution is maternal age. At ages 30-34 and >34, the percentages of mothers who delivered at Camp Lejeune were approximately 7.5% and 2%, respectively (ATSDR 1998). Although maternal age has a skewed distribution in the study population, we could not match on this risk factor because we lacked information on maternal age for about 20% of the study population.

The order of preference for participants in the study is 1) the biological mother of the case or control child, 2) the biological father of the case or control child, or 3) the case or control child. If the biologic father is not the initial study respondent, we will also attempt to contact him to obtain more detailed information about his medical history, lifestyle habits, and occupational history.

Sample Size, Power, and Precision of Risk Estimates

For a sample size calculation, the values of the alpha error, beta error, and minimum meaningful effect size are selected, and the required sample size is calculated. However, since the number of exposed subjects and the total number of cases for each outcome cannot be increased, and the alpha and beta errors should be set as low as possible, the only parameter that can vary is the meaningful effect size. If the a.) alpha error

is set at 0.10 (i.e., 90% confidence interval) b.) beta error is set at 0.20 (i.e., 80% power) and c.) the expected exposure prevalence is 40%, the following ORs can be detected given the number of cases for each outcome:

- an OR of 4.3 or greater can be detected for 15 cases with NTDs and 450 controls and an OR of 2.85 or greater can be detected for 28 cases with NTDs and 448 controls,
- an OR of 3.5 or greater can be detected for 20 cases with oral cleft defects and 440 controls and an OR of 2.5 or greater can be detected for 36 cases with oral cleft defects and 432 controls, and
- an OR of 5.15 or greater can be detected for 12 cases with leukemia and 444 controls and an OR of 4.3 or greater can be detected for 15 cases with leukemia and 450 controls.

An exposure prevalence of 40% is from the previous study of SGA at Camp Lejeune (ATSDR 1998; Sonnenfeld et al. 2001). It represents the percent of births born at Camp Lejeune that were estimated to ever have been exposed to PCE during the study period. Although we will not know for sure until after the water modeling is completed, it is expected that about half of the births were exposed to PCE. It is also expected that the levels of exposure to PCE varied over the study period such that there will be a significant range of exposures to PCE. The situation for TCE is less clear, and probably a large majority of the births were not exposed to TCE. Again, the TCE levels will vary over the study period so there will be a range of exposures.

All 79 children with the following confirmed or pending birth defects and childhood cancers who were born to parents residing at Camp Lejeune during their pregnancy between 1968 and 1985 will be recruited for the study: 28 NTDs, 36 oral cleft defects, and 15 leukemias. We expect a 90% participation rate because all of the participants took part in the Camp Lejeune Survey in 1999-2002 and gave permission to be contacted for future studies. Additionally, many survey participants have telephoned ATSDR to request the results of the survey and inquire about future studies. A 90% participation rate will yield 71 cases: 25 NTDs, 32 oral cleft defects, and 14 leukemias. Using one control group, we will attempt to enroll ten times as many controls as cases which will yield a comparison group of 710 children to allow

enough controls for the analyses.

Enrollment of Study Participants

The informed consent for the 1999-2002 ATSDR survey (IRB No. 2544) included a clause that ATSDR or their representative may contact the participants to ask them to take part in future studies (Appendix III). Potential participants will be informed about the study by an initial contact letter describing the purpose and design of the study (Appendix IV). Two weeks after the letters are mailed out; contractors will call the potential participants and invite them to take part in the study by participating in a 45 minute long telephone interview. If the initial study participant is not the child's father, we will also attempt to contact the child's father so we can get more detailed information about the father's medical history, lifestyle habits, and occupational history.

Data Collection

Trained interviewers will administer a telephone questionnaire using a computer-assisted telephone interview (CATI) instrument. The questionnaire will be administered to the biological mother of the case or control child; questions that ask about the biological father's lifestyle habits and medical and occupational history during the time period of interest will also be administered to the biological father if available to obtain more detailed information. A verbal informed consent will be obtained before the first question is read (Appendix V). The questionnaire will collect information on demographic and personal characteristics such as mother's residential history for a one year period before and after the birth of the index child; maternal drinking water and other home water usage; mother's pregnancy history of the index child (fever, prenatal care, medications, etc.); parental history of birth defects or having a previous child with a birth defect; maternal smoking, alcohol use, and occupation; and father's lifestyle habits and occupational history (Appendix V). Select variables collected in the 1998 study and the subsequent 1999-2002 survey (i.e., maternal residential history, child's date of birth, and highest level of education) will be pre-loaded into the CATI instrument and verified with the respondent. The collected information will be used to assign exposure status and to assess potential confounding.

A training manual describing interviewing techniques, intent and instructions for each question, and

how to avoid introducing bias during the interview will be provided to interviewers. Interviewer training will also include administering the questionnaire to other interviewers under observation by staff familiar with the study protocol. All completed interviews will be checked for completeness, consistency, and errors.

Human Subjects and Confidentiality

The Centers for Disease Control and Prevention (CDC) and ATSDR Privacy Act Officer has reviewed this IRB application and has determined that the Privacy Act is applicable. The contractor must verify full names and locating information on respondents because certain information (maternal residential history, date of birth, race) must be verified or obtained in order to conduct the study and analyze the data. Additionally, further studies may be conducted on children who were born to parents who resided at Camp Lejeune during their pregnancy between 1968 and 1985. Records will become part of the ATSDR Privacy Act system of records 09-19-0001, "Records of Persons Exposed or Potentially Exposed to Toxic or Hazardous Substances."

Under the Privacy Act of 1974 (5 U.S.C. Section 552(e)), employees of federal agencies are responsible for protecting data collected on identifiable persons or organizations where the supplier of information has not given the agency consent to make that data public. This responsibility for protection includes unauthorized visual observation of confidential material, accidental loss, and theft of data. Accordingly, confidential records will be kept out of sight of unauthorized persons, stored in locked cabinets or locked in rooms when not being used, copied only when absolutely necessary, and stored in sealed containers when transferred to archives. To assure privacy and confidentiality, each participant will be assigned a unique identification number that will be placed on the questionnaire, consent forms, and any other information collected from the participant. Individual identification numbers only will appear on all forms. Computerized data analysis files will contain identification numbers only.

The questionnaire will be administered as a computer-assisted telephone interview. Safeguarding measures will include limiting access to files to a small number of authorized staff, password protecting computer files, and utilizing a computer system with security measures that protect information against accidental loss and theft. Privacy Act clauses will be included in the contract to protect against

inappropriate data disclosures.

The study is performed solely for the purpose of developing or contributing to generalizable knowledge. There are no physical risks involved. No social, economic, legal or other risks are anticipated. Questions that ask about birth defects and childhood cancers may be sensitive to some individuals, but are not more than minimal risk. Information about outcome of pregnancies and birth defects could also be considered sensitive information. The questionnaire will be reviewed by the CDC/ATSDR IRB prior to being administered to participants. Interviewers will be trained to deal with individuals that have emotional reactions.

Although we are requesting a waiver of documentation of informed consent (see below), respondents will be informed that providing the requested information is entirely voluntary and informed consent will be obtained verbally. Reports of statistics derived from confidential data will be presented in such a way as to avoid inadvertent disclosure about specific study subjects. Final reports from this study will not contain medical information or findings in association with any individual subject. All records will continue to be maintained in compliance with the Privacy Act of 1974.

Requested Waivers

We are requesting a waiver of documentation of informed consent according to 45 CFR 46.117(c)(2) because the research represents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. This telephone survey takes approximately 45 minutes and obtains mostly non-sensitive information on demographic characteristics, pregnancy history, parental occupations, and lifestyle habits.

Quality Control

All electronically entered information obtained from questionnaires will be reviewed for missing data and ambiguous responses. Individual interviewers will be contacted to complete missing data where possible or to call back participants to fill in the missing information. Internal consistency and validity programs will be used to identify and correct coding and data entry errors. Data entry will be verified for accuracy by using software data match features.

Reimbursement

No remuneration will be offered to participants. In addition, no invasive procedures will be performed which could potentially cause injury or the need for medical treatment.

Data Analysis

The exposure variables include exposure status, concentration level, and/or percent of water from a contaminated source during specific time periods of interest in the one-year period before the child's birth. TCE and PCE will be evaluated separately. The exposure metrics will be ever/never, a categorization of the contaminant levels, and a categorical exposure variable that incorporates water usage and consumption as well as contaminant levels. Categorical exposure variables will be used because of the uncertainties involved in estimating exposures. We will look at the distribution of contaminant levels to determine appropriate cutoff values for the categorical variables. Those exposed to TCE or PCE will be compared to those without exposure to either chemical in the drinking water. Extensive sensitivity analyses will be conducted on the water modeling.

Descriptive statistics will be presented for the potential risk factors. Verified cases of birth defects and childhood cancers will be compared with controls using unconditional logistic regression. It may be necessary to use exact or conditional logistic regression methods if the data are too sparse. We will consider doing a secondary analysis including unconfirmed cases because the true odds ratio lies between the results obtained by analyzing only confirmed cases and confirmed and unconfirmed cases because unconfirmed cases are not all negative (do not have the condition) or all positive (do have the condition).

Each type of birth defect or cancer will be analyzed separately. Unadjusted and adjusted results will be computed, and 90% confidence intervals will be calculated for the parameter estimates. Potential confounders will be entered individually in the regression model with the exposure status. Variables that contribute to a change in the parameter estimate of the exposure status of 10% or more will be included in the final adjusted model. Adjusted results will only be presented if the adjusted and unadjusted results differ by more than 10%. SAS (Statistical Analysis Software) or SPSS will be used to generate the odds

ratios and confidence intervals.

Secondary or exploratory analyses will attempt to evaluate possible effect modification by sex, race/ethnicity, maternal age, smoking, and SES factors. However, sparse data may preclude such analyses. We will also attempt to evaluate in the exploratory analyses whether leukemia risk is associated with exposures during the first year of life.

We will not base our interpretation of the findings solely on statistical significance testing; instead, interpretation of the findings will be based on the magnitude of the association (i.e., the size of the odds ratio) and the exposure-response relationship.

Dissemination of Results

ATSDR will publish a final report of the study which will be distributed to the general public. Additionally, a presentation will be made at the United States Marine Corps Base in Camp Lejeune, North Carolina; the presentation will be made available to the public using a web broadcast. After the data is analyzed and final report is produced, we will collaborate with NCEH/ATSDR's Office of Communication to help us develop appropriate messages for pregnant women who conceived while living at Camp Lejeune during 1968-1985. However, our general communication plan, including strategy and messages, is described in the following paragraphs.

The strategy for communicating the results of the case-control study will be similar to the approach used to communicate the results of the survey progress report. Study participants will be mailed a copy of the Executive Summary from the final report and a letter providing estimates of the level of chemicals they were exposed to in drinking water (Appendix IX). Because the study population is dispersed over a wide geographic area, ATSDR will develop a web broadcast that discusses the results of the study. Study participants will be mailed a letter that provides the internet address for the web broadcast and also tells them how to receive a copy of the web broadcast on CD-ROM if they do not have internet access. ATSDR will update our Camp Lejeune website to include the full final study report as well as a link to the web broadcast. If study participants or other interested parties have questions about the study, they can email or call ATSDR. ATSDR will set-up a response line staffed with operators who are

dedicated to answering questions about the study. The operators will also respond to emails. Telephone operators will receive extensive training on how to respond to calls and emails including response line procedures, frequently asked questions, and when to triage calls/emails to study investigators.

Communicating results of environmental epidemiology studies to the general public is often complicated and challenging. Scientific concepts may be difficult for the general public to understand and there may be trust issues between the community and the federal government. To overcome these challenges, study participants will be informed of how ATSDR measured associations and the criteria used to interpret the meanings of the associations. Specifically, that odds ratios and confidence intervals were calculated for the different outcomes (birth defects and childhood cancer). Odds ratios compare the proportion of cases exposed to the proportion of controls exposed. If the proportions are the same (i.e., 1), there is no association between the exposure and the disease. If the proportion is higher in the cases (i.e., greater than 1), there is an association between exposure and disease. Confidence intervals assess the variability and precision of the odds ratio. The width of the confidence interval reflects the amount of variability in the odds ratio. Wider confidence intervals are less precise; narrower confidence intervals are more specific but less certain that the true odds ratio is within the confidence interval. If the confidence interval includes 1, then it is possible that the measured association was due to chance. The criteria used to interpret the meanings of those associations include:

- the strength of the association (the magnitude of the odds ratio),
- the consistency of findings, both within the study and when compared to other epidemiologic studies,
- dose-response effect (as concentration of TCE/PCE and/or the amount of water consumed increases, so does the risk of having a birth defect or childhood cancer), and
- when the exposure occurred the pregnancy and the duration of the exposure.

DISCUSSION

This is the first study to examine the associations between specific birth defects and childhood leukemia and exposures to VOCs in drinking water at Camp Lejeune. The proposed study has limitations and steps will be taken to reduce bias when possible. Efforts have been made to achieve a complete

ascertainment of all cases of NTDs, oral clefts, and ALL. Even though the survey achieved a high participation rate of almost 80% of the total pregnancies that occurred at Camp Lejeune during the study period, the rates of birth defects and childhood cancers among the remaining 20% who did not participate is unknown (ATSDR 2003). The process of confirming the diagnoses of the potential cases is still ongoing. ATSDR will make the utmost efforts to enroll all confirmed cases in this study. Selection bias due to a low participation rate is not a potential problem, but confirming as many potential cases as possible will be key to the success of this study.

Computer modeling of the drinking water system at Camp Lejeune during 1968-1985 will provide ATSDR with extensive exposure information that is as accurate as possible. Errors in the recall of maternal residential address on base during pregnancy will not be a problem because housing records will be used to determine maternal residential address. However, recall bias is possible during the collection of historical water consumption and use habits. Additionally, recall of potential confounders may not be accurate because the time period of interest is 28-35 years in the past. To aid in the recall, participants will be prompted with specific activities associated with water consumption and use and with potential confounders.

To prevent interviewer bias, interviewers will be trained to adhere to the exact wording of the questionnaire. Interviewers will also be monitored on a regular basis during the administration of interviews to assure consistency. Furthermore, interviewers will not be aware of the case-control status of a subject and will be blinded regarding exposures status. Participants are interviewed on first contact when willing to do so. Interviewers will attempt to contact participants at different times of the day and different days of the week to minimize loss through non-contact.

The current study is likely to be constrained by a small sample size which would limit both the statistical power of the study to detect associations between in utero exposure to VOCs in drinking water and birth defects and childhood cancers and the ability to make inferences to other populations of pregnant women exposed to VOCs in drinking water. A small sample size will also likely result in wide confidence intervals of the effect measure.

While there is no direct public health benefit to those children potentially harmed by the

contaminated drinking water at Camp Lejeune, the information gained during the study will help advance research on this topic and may help future children. Only a small number of studies have looked at the risk of birth defects and childhood cancers among children born to mothers exposed during pregnancy to volatile organic compounds (VOCs) in drinking water.

This study is unique in that it will examine the associations between well-defined exposures to TCE/PCE in drinking water and risk of developing specific birth defects and childhood leukemia. The associations between exposure to TCE/PCE during various time periods of interest (pre-conception/trimesters/entire pregnancy) and the risk of particular health outcomes can be thoroughly examined.

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Table 1- Risk Factors for Specific Birth Defects and Childhood Leukemia

Health Condition	Risk factor	OR (CI or Range*)	References
Cleft lip and palate	Maternal smoking	1.20-3.33	Khoury et al. 1987 Wyszynski et al. 1997 Chung et al. 2000
	Maternal alcohol consumption	3.0 (1.1-8.5)	Werler et al. 1991
	Maternal folic acid intake	0.52 (95% CI:0.34-0.80)	Itikala et al. 2001
	Maternal occupational exposures	2.5-13.0	Lorente et al. 2000 Khattaak et al. 1999
	Birth order – 4 th or later child	3.35 (95% CI: 2.39-4.69)	Viera & Orioli 2002
Neural Tube defects	Maternal folic acid intake	RR: 0.11 (0.02-0.66) 0.41 (95% CI: 0.26-0.66)	Smithells et al. 1981 Mulinare et al. 1988
	Maternal Occupational exposure	1.3-5.6	Shaw et al. 2001 Brender et al. 2002 Blatter et al. 1996
	Maternal fever	1.91 (95% CI: 1.35-2.72)	Shaw et al. 1998
	Maternal use of valproic acid	20.6 (95% CI: 8.2-47.9)	Robert & Guibaud 1982
Leukemia	TCE & PCE contaminated drinking water	RR: 1.43 (95% CI: 1.07-1.90) 8.33 (95% CI: 0.73-94.67)	Cohn et al. 1994 Costas et al. 2002
	Down's syndrome	20.0 (95% CI: 4.2-94.2)	Aver-Loisau et al 1995 Cnattingius et al. 1995
	Ataxia-telangiectasia	SIR: 37 (95% CI:13-80)	Olsen et al. 2001
	High birth weight	1.09 (95% CI:0.90-1.31)	Reynolds et al. 2002
	Maternal smoking Paternal smoking	0.66 (95% CI:0.46-0.94) 1.56 (95% CI:1.03-2.36)	Shu et al. 1996 Adami et al. 1998
	Maternal alcohol consumption	1.43 (95% CI:1.00-2.04)	Shu et al. 1996
	Radiation	1.4 (95% CI:0.9-2.3)	Shu et al. 1988
	Electric Magnetic Fields	1.24 (95% CI: 0.86-1.79)	Linnet et al. 1997