Morbidity Study of Former Marines, Dependents, and Employees Potentially Exposed to Contaminated Drinking Water at USMC Base Camp Lejeune

Study Protocol
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PROJECT OVERVIEW

Protocol Summary

From the 1950s through the mid-1980s, persons residing or working at the U.S. Marine Corps Base Camp Lejeune, North Carolina were potentially exposed to drinking water contaminated with volatile organic compounds (VOCs). The heavily contaminated wells were shut down in February 1985.

On January 28, 2008, President Bush signed H.R. 4986: National Defense Authorization Act for Fiscal Year 2008. The Act requires ATSDR to develop a health survey of persons possibly exposed to contaminated drinking water at Camp Lejeune that would collect personal health information. The Act further states that the collection of this health information could provide a basis for further scientific studies of potentially adverse health impacts of exposure to contaminated water at Camp Lejeune. The Act requires the survey to be developed within 120 days of enactment and to be conducted within one year of enactment.

The study population for the morbidity study will include the following: (1) Marine and Navy personnel stationed at Camp Lejeune any time during the period June 1975 to December 1985, (2) civilians who worked at Camp Lejeune anytime during the period December 1972 to December 1985, (3) parents and children (who were born prior to 1986 and who are now adults) included in a 1999-2002 ATSDR survey for whom a current address can be found; and (4) a random sample of active duty and civilian workers who were stationed at Camp Pendleton during June 1975- December 1985 and December 1972-

December 1985, respectively, and were not stationed at Camp Lejeune during the period of drinking water contamination. The morbidity study population will be identified from available data from the Defense Manpower Data Center (DMDC) personnel records and the ATSDR 1999-2002 survey data. DMDC data are not available to identify base locations for active duty personnel before June 1975, and DMDC data for civilian employees are not available before December 1972. Health surveys will be mailed to those for whom a current address can be found. Personal identifier information (i.e., name, date of birth, and social security number [SSN]) will be used to obtain current addresses.

The health survey instrument will collect information on cancers and the following non-cancer diseases of interest: Parkinson's disease, kidney failure and other severe kidney diseases, severe liver diseases, lupus, aplastic anemia, TCE-related skin disorders, scleroderma, multiple sclerosis, motor neuron disease/amyotrophic lateral sclerosis, infertility and endometriosis. In addition, the health survey instrument will include questions on miscarriages occurring to women who were pregnant while residing or working on base. Information about potential confounders will also be collected. Cancers and non-cancer diseases will be confirmed by medical records, death certificates or cancer registrations.

The morbidity study will be conducted to assess whether there is an association between exposure to the contaminated water at Camp Lejeune and specific cancers and the other diseases of interest. Monthly average levels of drinking water contaminants at the residence will be the basis for the primary exposure variables. The monthly average contaminant levels at the Camp Lejeune residences of the study population will be based on the historical reconstruction of the movement of contaminants through the ground

water and into the distribution system. Ground water contamination fate and transport models and water distribution system models will be used to estimate historical monthly averages (and Monte Carlo 95% intervals) of contaminants in the Hadnot Point and Tarawa Terrace drinking water systems during the period when contaminated wells were in use. Because the water in each of these two systems was mixed at the treatment plants prior to distribution, the monthly average contaminant levels in the distribution systems of these systems accurately reflects the contaminant levels in the residences and workplaces served by each of these systems. The residential monthly average contaminant levels will provide the basis for the primary exposure variables: cumulative exposure, average exposure, maximum exposure, and duration of exposure.

To comply with the Congressional mandate, those who registered with the United States Marine Corps (USMC) will also be mailed the same health survey. However, those who were identified solely because they registered with the USMC will <u>not</u> be included in the morbidity study; their self-reported diseases will not be confirmed; and their completed health surveys will be analyzed separately, primarily in a descriptive manner.

Investigators & Roles/Funding Sources

The Principal Investigators will include Frank Bove and Perri Zeitz Ruckart. Both are epidemiologists within the Division of Health Studies at ATSDR. Westat (support award number GS-23-F-8144H, task order 200-2010-F-36799) was selected as the contractor to mail out the survey, develop the web portal for the web-based survey, trace and locate participants, manage medical records confirmation, obtain data from the cancer registries, and manage the data. Funding is being provided by Department of Defense (DOD); they are not engaged in the research in any manner, but will receive a final report

with aggregate data.

INTRODUCTION

The United States Marine Corps (USMC) Base at Camp Lejeune, North Carolina began operations during the early 1940s. Eight water treatment plants provided drinking water to family housing units and barracks at the base prior to March 1987: Tarawa Terrace (TT), Hadnot Point (HP), Holcomb Boulevard (HB), Courthouse Bay, Rifle Range, Onslow Beach, Montford Point/Camp Johnson and New River. Volatile organic compounds (VOCs) were detected in HP and TT wells and their water distribution systems during the base's 1980-85 sampling program. The primary contaminant in the TT system was tetrachloroethylene (also known as perchloroethylene or PCE), with the maximum detected level of PCE in the distribution system of 215 parts per billion (ppb). The primary contaminant in the HP system was trichloroethylene (TCE) with the maximum detected level of TCE in the distributions system of 1,400 ppb. Other major contaminants in the HP system included trans-1,2-dichloroethylene (DCE), PCE, and benzene. The most contaminated wells in the HP and TT systems were shut down by early February 1985.

An important feature of the contamination of these drinking water systems is its intermittent nature. Each system had many more wells than were necessary to supply water on any given day. Wells were rotated in and out of service and contamination levels in the drinking water distribution system varied depending on the wells being used at a particular time. In each system, water from all the wells in use was mixed before treatment and distribution.

The HP system was constructed in the 1940s, the TT system was constructed in 1952, and the HB system was constructed in June 1972. Prior to June 1972, the HB service area was supplied by the HP system. In addition, after June 1972 the HB system was

supplemented with water from the HP system during some weeks in the summer when water use was high. No organic solvent contamination was detected in the drinking water from the other treatment plants serving the base.

<u>1998 ATSDR Study of Adverse Birth Outcomes ("SGA study")</u>

The Agency for Toxic Substances and Disease Registry (ATSDR) conducted a study of live births to women who resided in base family housing at time of delivery during the period January 1, 1968 through December 31, 1985. Base family housing records were used to identify maternal residence(s) during pregnancy. Information from the birth certificate was used to determine birth weight and gestational age. The study found that "long-term" TCE exposure from HP 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 PCE from TT water was associated with elevated risk for SGA among infants born to mothers aged >35 years (adjusted OR=2.1, 90% CI: 0.9, 4.9) and among mothers with two or more prior fetal losses (adjusted OR=2.5, 90% CI: 1.5, 4.3) (Sonnenfeld et al. 2001).

<u>Current ATSDR Epidemiological Study of Specific Birth Defects and Childhood Leukemia</u>

ATSDR is currently conducting a study of birth defects and childhood cancers in children born from 1968 through 1985 to mothers who resided at the base anytime during their pregnancy. Potential cases were identified by a telephone survey of parents conducted by ATSDR during 1999-2002 and were verified using medical records. The phone survey obtained information about the child's health, the dates of birth of the mother and father, and the dates the parents resided at Camp Lejeune. In 2003, work began on the historical exposure reconstruction of the TT and HP systems.

A total of 106 cases were reported in the survey: 35 NTD, 42 oral clefts, and 29

childhood leukemia/NHL. Medical record confirmation was sought for all reported cases. Attempts were made to conduct phone interviews of medically confirmed cases and a random sample of births included in the 1999-2002 survey who did not have a birth defect or childhood cancer. Parent interviews obtained information on residential history on base, water consumption habits during pregnancy, and potential confounders. Of the 35 reported NTD, 15 were confirmed and the parents of all 15 were interviewed. Of the 42 reported oral clefts, 24 were confirmed and the parents of 23 were interviewed. Of the 29 reported childhood leukemia/NHL, 13 were confirmed and the parents of all confirmed cases were interviewed. In total, 52 of the 106 reported cases were confirmed and the parents of 51 of these confirmed cases were interviewed. Efforts were made to contact the parents of 651 control children and 548 (84.2%) were interviewed (for 87 of the controls, only the father could be interviewed).

When the water modeling is complete, we will link the water modeling data with the interview data to assign exposure status and contamination levels to the cases and controls. We expect the study to be completed in 2009.

Rationale for Morbidity Study

In 2005 a panel of independent scientists convened by ATSDR to explore opportunities for conducting additional health studies at Camp Lejeune made several recommendations, among them that the agency:

- Identify cohorts of persons with potential exposure, including adults who lived on base; adults who resided off base, but worked on base; children who lived on base; and those who may have been exposed while in utero; and

- Conduct a feasibility assessment to address the issues involved in planning

future studies of mortality, cancer incidence, and other health outcomes of interest at the base.

In response to these recommendations, ATSDR conducted a feasibility assessment which included convening a panel of epidemiologists with experience conducting studies of military and occupational cohorts to provide recommendations on future studies. Based on the recommendations of this panel and on research conducted for the feasibility assessment, ATSDR concluded that it is possible to evaluate cancer incidence and other diseases through a mailed health survey of those identified by the Defense Manpower Data Center (DMDC) personnel databases or the 1999-2002 ATSDR survey as having lived or worked at Camp Lejeune during the period of drinking water contamination (DMDC 2004).

On January 28, 2008, President Bush signed H.R. 4986: National Defense Authorization Act for Fiscal Year 2008. The Act requires ATSDR to develop a health survey of persons possibly exposed to contaminated drinking water at Camp Lejeune that would collect personal health information. The Act further states that the collection of this health information could provide a basis for further scientific studies of potentially adverse health impacts of exposure to contaminated water at Camp Lejeune. The Act requires the survey to be developed within 120 days of enactment and to be conducted within one year of enactment.

Study Objectives

The morbidity study will collect information on cancers, other diseases of interest, and information about potential confounders via a mailed health survey. Self-reported diseases will be confirmed by medical records, cancer registrations and death

certificates. The morbidity study will evaluate whether exposure to the contaminated

water at Camp Lejeune is associated with specific diseases of interest which were

selected based on a literature review of occupational and drinking water studies involving

solvent exposure. Except for miscarriages, only diseases confirmed by medical records,

death certificates or cancer registrations will be evaluated. Miscarriages will be

considered "confirmed" and included in the analyses only if the respondent indicates that

a positive pregnancy test occurred prior to the miscarriage and the miscarriage was

confirmed by a health provider.

To have an unbiased sampling frame, the study population for the morbidity study

will consist of those identified by computerized databases from the DMDC and ATSDR

as having lived or worked at Camp Lejeune during the period of drinking water

contamination. The study population will also include active duty Marines and civilian

employees randomly sampled from those stationed or employed at Camp Pendleton

anytime during June 1975-December 1985 and December 1972-December 1985,

respectively, and who were not stationed at Camp Lejeune during the period of drinking

water contamination. This comparison sample from Camp Pendleton will total 50,000

Marines and 10,000 civilians.

RISK ASSESSMENTS AND DRINKING WATER STANDARDS

The MCLs for TCE, PCE, and benzene are 5 ppb (or 5 µg/L); the MCL for vinyl

chloride is 2 ppb; and the MCL for DCE is100 ppb. The EPA calculated 10^{-6} cancer risk

for TCE, vinyl chloride and benzene are 3 ppb, 0.02 ppb, and 1 ppb, respectively.

California has set public health goals (PHGs) for these contaminants based on their

carcinogenicity (in animals and/or humans), or in the case of DCE, non-cancer endpoints

(California Environmental Protection Agency 1999, 2000, June 2001, August 2001). The

PHGs based on carcinogenicity correspond to a 10^{-6} cancer risk. The PHGs for TCE,

PCE, vinyl chloride, and benzene are 0.8 ppb (mice liver tumors), 0.06 ppb (liver cancer

in mice, leukemia in rats), 0.05 ppb (lung cancer in mice), and 0.15 ppb (leukemia among

workers). The PHG for DCE is 60 ppb based on kidney and liver effects in mice. For

chronic, non-cancer endpoints, the PHGs for TCE, PCE, vinyl chloride and benzene are

1000 ppb (kidney effects in rats), 11 ppb (neurobehavioral effects in humans), 3 ppb

(liver effects in rats) and 26 ppb (hematological effects in refinery workers).

LITERATURE REVIEW ON HEALTH EFFECTS OF VOC-CONTAMINANTS

Chronic Adult Health Effects of the VOC-Contaminants

Virtually all of the studies of human health effects of these chemicals are

occupational studies. Adult cancer risks have been studied in only two populations

(northern NJ and upper Cape Cod, MA) exposed to public drinking water contaminated with

PCE (Aschengrau et al. 1993; Aschengrau et al. 1998; Aschengrau et al. 2003; Paulu et al.

1999; Fagliano et al 1990; Cohn et al. 1994). Only one population (northern NJ) exposed to

TCE-contaminated public water supplies has been studied for adult cancer risk (Fagliano et

al 1990; Cohn et al. 1994). No studies have been conducted of medically confirmed, non-

cancer adult diseases and exposure to solvent-contaminated, public drinking water supplies.

One public drinking water study in Denver, CO utilized a neurobehavioral test battery to

evaluate effects of exposures to organic solvents (Reif et al. 2003).

Trichloroethylene (TCE)

Depending on water consumption patterns (e.g., length of showering or bathing,

other hot water uses), the dermal and inhalation routes of exposure to TCE-contaminated

drinking water contribute internal doses similar to ingestion and their total contribution is greater than that from ingestion (Weisel and Jo 1996; WHO 2005).

The National Toxicology Program's 11th Report on Carcinogens has stated that TCE is "reasonably anticipated to be a human carcinogen" based on "limited evidence" from human studies, "sufficient evidence" from animal studies (multiple sites or organs in multiple species), and "information suggesting TCE acts through mechanisms that indicate it would likely cause cancer in humans." The World Health Organization International Agency for Research on Cancer (IARC) classifies TCE as a probable (Group 2A) human carcinogen.

These occupational studies were evaluated in published meta-analyses (Wartenberg et al. 2000; Mandel et al. 2006; Alexander et al. 2006; Alexander et al. 2007) and an NAS report (NAS/NRC 2006). One drinking water study evaluated contamination by TCE and other VOCs in the municipal water supplies of 75 northern NJ towns and hematopoietic cancers (Cohn et al. 1993, Cohn et al. 1994). The maximum monthly average of TCE in any of the 75 towns was 55 ppb (Bove et al. 1995).

In 2006, the National Academy of Sciences/National Research Council, Committee on Human Health Risks of Trichloroethylene, issued its report, Assessing the Human Health Risks of Trichloroethylene (NAS/NRC 2006). For **lung cancer**, the NAS report concluded: "Results of most epidemiologic studies of occupational exposure to trichloroethylene do not show a strong association between trichloroethylene exposure and increased incidence of lung tumors. Thus, pulmonary cancer does not appear to be a critical end point in assessing human health risks to trichloroethylene."

The NAS report found that TCE and some of its metabolites were **nephrotoxic**

and **nephrocarcinogenic**. However the amount of exposure necessary to cause these effects is not known. The report concluded: "Evidence from experimental, mechanistic, and epidemiologic studies supports the conclusion that trichloroethylene is a potential kidney carcinogen." In a published meta-analysis of TCE (Wartenberg et al. 2000), the relative risk (RR) for kidney cancer was estimated at 1.7 (95% CI: 1.1-2.7).

For **liver cancer**, the NAS committee concluded: *"Exposure to trichloroethylene at concentrations relevant to the general public is not likely to induce liver cancer in humans. However, it is possible that much higher exposures to trichloroethylene, such as in certain high-risk occupations or in heavily contaminated locales, could result in increased risks of liver toxicity and cancer. In addition, the existence of sensitive populations due to genetics, disease, or life stage cannot be discounted."*

Two meta-analyses have been published for TCE and **liver cancer**. In the earlier meta-analysis, the estimated average SIR for three liver cancer incidence studies was 1.9 (95% CI: 1.0-3.4). The meta-analysis concluded that the evidence for a causal association for liver cancer was "moderate" and consistent. A recent meta-analysis (Alexander et al. 2007) combined mortality and incidence studies and obtained a summary RR of 1.41 (95%CI: 1.06-1.87) for primary liver cancer.

Two meta-analyses have been published for **non-Hodgkin's lymphoma** (NHL) and TCE exposure (Wartenberg et al. 2000; Mandel et al. 2006). In addition, a NJ drinking water study evaluated TCE-contaminated drinking water and the incidence of NHL (Cohn et al.. 1994). The earlier meta-analysis (Wartenberg et. al. 2000) obtained an average SIR for NHL incidence of 1.5 (95% CI: 0.9, 2.3). The authors concluded that the evidence for a causal association was "moderate" and consistent. The later meta-analysis

(Mandel et al. 2006) obtained a summary RR of 1.86 (95% CI: 1.27-2.71) for NHL incidence for studies that identified a specific TCE exposed sub-cohort. The NJ drinking water study (Cohn et al. 1994) reported sex-specific SIRs for total NHL and for each NHL grade (low, intermediate, high). TCE levels in the municipal drinking water supplies for 75 towns in northern NJ were categorized as below detection (<0.1 ppb), 0.1 ppb to 5 ppb, and >5 ppb. Because the SIRs were similar for males and females, SIRs for males and females combined were calculated for this feasibility assessment using the data supplied in the state report (Cohn et al. 1993). For TCE levels >5 ppb, the SIRs for total NHL and high grade NHL (excluding Burkitt's lymphomas) were 1.28 (95% CI: 1.08-1.50) and 2.61 (95% CI: 1.22-5.54), respectively. SIRs increased with increasing NHL grade and increasing level of TCE contamination in the drinking water.

Adult leukemia was not found to be associated with TCE occupational exposures in the meta-analyses. In the NJ drinking water study (Cohn et al. 1993, 1994), at TCE levels >5 ppb, the SIR for total leukemias (calculated for this feasibility assessment) was 1.23 (95% CI: 1.02-1.50). For chronic lymphocytic leukemia, the SIR was 1.52 (1.10-2.12). For the other types of leukemia, there were either large differences between males and females or the sex-specific SIRs hovered around 1.0. One notable finding was a very high SIR for childhood acute lymphocytic leukemia (ALL) among females diagnosed before 5 years of age: 4.54 (95% CI 1.47-10.6), based on 5 cases. The Woburn study (Costas et al. 2002) also found a high risk of ALL especially among those exposed in utero, but the majority of the cases were male. Being served primarily by wells G and H (267 ppb TCE, <25 ppb PCE and DCE) during pregnancy was associated with childhood leukemia (OR=8.3, 95% CI: 0.7, 94.7).

Multiple myeloma was not associated with TCE exposure in one meta-analysis (Alexander et al. 2006). A second meta-analysis found weak evidence supporting an association (Wartenberg et al. 2000). The average SIR and SMR were estimated at 1.5 (95% CI: 0.7-3.3) and 1.9 (95% CI: 1.0-3.7), respectively.

Only 2 occupational studies evaluated **cervical cancer** (Wartenberg et al. 2000). An SIR of 2.4 (95% CI: 1.2-4.8) and an SMR of 1.8 (95% CI: 0.5-6.5) were reported in these studies. **Hodgkin's disease** was evaluated in 6 studies. The average SIR and SMR estimated in a meta-analysis (Wartenberg et al. 2000) was 1.5 (95% CI: 0.6-3.7) and 2.0 (95% CI: 1.1-3.4). **Prostate cancer** was evaluated in 7 studies with an average SIR and SMR of 1.3 (95% CI: 1.0-1.6) and 1.2 (95% CI: 1.0-1.4), respectively (Wartenberg et al. 2000). **Other cancers** (bladder, breast, brain, colon, rectum, esophagus, lung, and pancreas) were not found to be associated with TCE occupational exposure in the meta-analysis (Wartenberg et al. 2000).

A cluster of 3 cases of **Parkinson's disease** and 14 cases of Parkinsonism in a small industrial plant producing small instruments were evaluated (Gash et al. 2007). All the workers worked for many years in the vicinity of degreasing operations where TCE was used. A concurrent animal study indicated a possible mechanism involving loss of dopamine neurons together with impaired complex I activity in the substantia nigra after TCE exposure (Gash et al. 2007). In another study, three cases of Parkinson's disease with a history of industrial exposure to TCE were evaluated (Kochen et al. 2003). The NAS report on TCE recommended further research in this area (NAS/NRC 2006).

Occupational and drinking water exposures to TCE have been associated with the **autoimmune diseases, scleroderma and lupus** with similar effects seen in animal

studies (Cai et al. 2008; Wang et al. 2007). A meta-analysis of case-control studies of workers exposed to organic solvents (not otherwise specified) obtained summary odds ratios for scleroderma for males (OR=3.0; 95% CI: 1.9-4.6) and females (OR=1.8; 95% CI: 1.2-2.5) indicating males are at higher risk although most cases are among female workers (Kettaneh et al. 2007). Occupational exposure to TCE has also been associated with **generalized skin disorders and accompanying hepatitis** (e.g., Stevens-Johnson syndrome) similar to drug-induced hypersensitivity syndrome (Goh and Goon 2008; Kamijima et al. 2007; Li et al. 2007; Nakajima et al. 2003). The skin rash occurs typically on the extremities, face, neck or trunk within a few months of occupational exposure, and it can reoccur after minimal re-exposure. Some cases did not use TCE but worked close to the degreasing operations suggesting that skin contact with TCE is not necessary (Kamijima et al. 2007).

Chronic occupational exposure to TCE has been associated with non-cancer **liver disease** such as hepatic necrosis, fatty liver, and cirrhosis (NAS/NRC 2006). There is also some evidence in animal studies and occupational studies that TCE can cause non-cancer **kidney disease**, in particular tubular proteinuria.

The NAS report evaluated the studies of **male and female reproductive effects** and concluded that the findings in animal studies indicated that TCE was "toxic to spermatogenesis and sperm fertilizing ability" as well as adversely affected the fertilizability of female oocytes, although it was unclear whether the effects were transient or permanent and whether they were relevant to humans (NAS/NRC 2006). In rodent studies, TCE exposure damaged epididymal epithelial cells and sperm (Kan et al. 2007). In an occupational study, TCE and PCE exposures were linked to reduced fertility

among female workers (Sallmén et al. 1995). Studies of miscarriage and occupational

TCE exposure have been inconclusive (NAS/NRC 2006).

In summary, based on the evidence from occupational and drinking water studies

of TCE exposure, several cancers and other diseases should be evaluated in future studies

at Camp Lejeune: kidney diseases, kidney cancer, liver diseases, liver cancer, NHL,

chronic lymphocytic leukemia, multiple myeloma, cervical cancer, Hodgkin's disease,

Parkinson's disease, autoimmune diseases such as scleroderma and lupus, and skin

disorders. Based on the animal evidence, infertility in males and females should also be

evaluated.

Tetrachloroethylene (perchloroethylene or PCE)

As with TCE, the dermal and inhalation routes are also important for drinking

water exposures to PCE (Franco et al. 2007). Most of the epidemiological studies of PCE

exposure have been on dry cleaning workers. A meta-analysis conducted for TCE also

evaluated studies of dry cleaning worker cohorts (Tier III studies in Wartenberg et al.

2000). A review of the epidemiological literature on PCE occupational exposures and

cancers has also been published (Mundt et al. 2003).

Drinking water studies in Cape Cod, MA and northern NJ evaluated PCE-

contaminated drinking water and specific cancers (Aschengrau et al. 1993; Paulu et al.

1999; Aschengrau et al. 1998; Aschengrau et al. 2003; Fagliano et al. 1990; Cohn et al.

1993; Cohn et al. 1994). In the upper Cape Cod areas, PCE leached into drinking water

from the inner vinyl lining of certain asbestos cement water distribution pipes, and levels

of PCE were as high as 80 ppb in higher-use areas and as high as 7,750 ppb in dead end

or low-use areas (Aschengrau et al. 1993; Paulu et al. 1999; Aschengrau et al. 1998;

Aschengrau et al. 2003). In the more recent northern NJ study, the maximum monthly average of PCE in the municipal water supplies of any of the 75 towns was 26 ppb (Cohn et al. 1993; Cohn et al. 1994). Some towns had a mixture of VOC contaminants (e.g., TCE and PCE) in their municipal supplies. Another study evaluated drinking water contaminated with a mixture of TCE, PCE and their degradation products and neurobehavioral effects (Reif et al. 2003).

The National Toxicology Program's 11th Report on Carcinogens has stated that PCE is "reasonably anticipated to be a human carcinogen" based on "limited evidence" from human studies, and "sufficient evidence" from animal studies. The NTP report concluded that based on studies of dry cleaning workers, "there is evidence for consistent positive associations between tetrachloroethylene exposure and esophageal and cervical cancer and non-Hodgkin's lymphoma." The "sufficient evidence" from animal studies included PCE associations with liver tumors and liver damage, kidney tumors and kidney damage, and leukemia.

A review of studies of PCE occupational exposures and **oral cancer** concluded that the evidence for an association was "limited" and "unlikely" due to inconsistent findings across studies, no associations in the case-control studies, and the inability to adjust for smoking and alcohol in the cohort studies (Mundt et al. 2003). The average SMR across 4 dry cleaner cohort studies for buccal cancer was 1.2 (95% CI: 0.7-2.1) (Wartenberg et al. 2000).

The average SMR for **esophageal cancer** across 3 cohort studies of dry cleaners was 2.2 (95% CI: 1.5-3.2) (Wartenberg et al. 2000). One review concluded that the evidence was "inadequate for firm conclusions" but "elevated risk estimates from the

large dry-cleaner cohorts likely to have PCE exposure cannot be dismissed, especially in the light of adequate latency and duration" (Mundt et al. 2003). Another review emphasized the consistent positive findings in the occupational studies (WHO 2006).

No associations were observed in cohort studies of dry cleaning workers and **liver cancer**. A recent case-control study also found no association (Lynge et al. 2006). Two reviews concluded that the evidence does not support a relationship between liver cancer and PCE exposure (Mundt et al. 2003; WHO 2006).

Excess mortality due to **pancreatic cancer** was reported in several cohort studies of dry cleaning workers with an average SMR of 1.3 (95% CI: 1.0-1.7); and one dry cleaning cohort study reported an excess in incidence (males: SIR=2.4; 95%CI: 1.1-4.5; females: SIR=1.4; 95%CI: 0.7-2.4) (Wartenberg et al. 2000). One review concluded that an association between PCE and pancreatic cancer was "unlikely" because other solvents may have caused the observed excess in one of the cohort studies and because the cohort studies could not adjust for potential confounders such as smoking (Mundt et al. 2003). In the Cape Cod drinking water study, no association was found between exposure to PCE-contaminated drinking water and pancreatic cancer.

Two cohort studies of dry cleaning workers evaluated **laryngeal cancer** mortality and the average SMR was 1.6 (95% CI: 0.7-3.5) based on a total of five cases (Wartenberg et al. 2000). One review concluded that the available evidence is "not adequate for firm conclusions" (Mundt et al. 2003).

The average SMR for cohort studies of dry cleaning workers and **lung cancer** was 1.3 (95% CI: 1.1-1.5) (Wartenberg et al. 2000). Although consistent, positive associations were observed across the studies, one review concluded that the evidence

was "limited" and a strong association "seems unlikely" because large excesses were not consistently observed and the cohort studies did not adjust for smoking (Mundt et al. 2003). In the Cape Cod drinking water study, exposure to PCE was associated with elevated lung cancer incidence in the highest exposure group, with adjusted odds ratios ranging from 3.7 (95% CI: 1.0-11.7) ignoring latency period to 19.3 (95% CI: 2.5-141.7) when a latency period of 9 years was assumed (Paulu et al. 1999).

The average SMR for cohort studies of dry cleaning workers and **cervical cancer** was 1.7 (95% CI: 1.5-2.0) (Wartenberg et al. 2000). Despite consistent, positive findings in the mortality studies, one review concluded that an association "seems unlikely" because the evidence for a mechanism and biological plausibility was "weak", and studies could not adjust for known risk factors (Mundt et al. 2003). On the other hand, another review emphasized the consistency in the positive findings (WHO 2006).

Consistent, elevated excesses of **bladder cancer** have been observed across several cohort and case-control studies of dry cleaning and laundry workers (Mundt et al. 2003; Wartenberg et al. 2000). The average SMR across the cohort studies of dry cleaning worker was 2.0 (95% CI: 1.3-2.9) (Wartenberg et al. 2000). However, one review concluded that the evidence was "inadequate" because of the lack of confounder adjustment in the cohort studies and the lack of clear exposure-response relationships (Mundt et al. 2003). On the other hand, the Cape Cod drinking water study found an association between PCE and bladder cancer incidence (adjusted OR=4.03; 95% CI: 0.65-25.10). There were too few cases of bladder cancer to account for a latency period (Aschengrau et al. 1993).

Heterogeneous results across cohort and case-control studies were observed for

kidney cancer. The average SMR across four cohort studies of dry cleaning workers was 2.3 (95% CI: 1.5-3.5), but no association was observed in the two cohort studies that evaluated kidney cancer incidence (Wartenberg et al. 2000). One review concluded that "it seems unlikely that a strong association exists" but that a definitive conclusion is not possible due to the small numbers of cases in the studies and the inconsistency of results across the studies (Mundt et al. 2003). In the Cape Cod drinking water study, no association was found for kidney cancer incidence (Aschengrau et al. 1993).

The results of cohort studies of dry cleaning workers have not suggested associations between PCE exposure and **non-Hodgkin's lymphoma (NHL) or leukemia**. One review concluded that the evidence is insufficient to determine whether a relationship exists between PCE exposure and hematopoietic cancers (Mundt et al. 2003). Two drinking water studies have found associations between PCE exposure and hematopoietic cancers. In the Cape Cod study, leukemia was associated with the >90th percentile levels of PCE drinking water contamination (accounting for latency, the adjusted OR = 5.84; 95% CI: 1.37-24.91) (Aschengrau et al. 1993). NHL was not evaluated in the Cape Cod study. In the northern NJ study, no association was found for leukemia, but an association was found with high grade NHL among women only (SIR=2.74; 95% CI: 1.20-6.26) (Cohn et al. 1994).

Cohort studies of dry cleaning workers found no associations with **breast cancer, prostate cancer, brain cancer or skin cancers**. In the Cape Cod drinking water study, no associations were found for brain cancer, however an excess of **breast cancer** was observed among those exposed to >90th percentile PCE levels (adjusted OR accounting for a latency period of 9 years = 1.9; 95% CI: 0.8-4.4) (Aschengrau et al. 2003).

In one dry cleaning worker study, an excess of **colon cancer and rectal cancer** was seen only among those workers exposed to PCE and other solvents, not among workers exposed only to PCE (Mundt et al. 2003). In the Cape Cod drinking water study, excesses of **colon and rectal cancer** were observed, but the strongest finding was for rectal cancer (adjusted OR for 13 years latency = 3.1; 95% CI:0.7-10.9) (Paulu et al. 1999).

Liver is a target organ for PCE exposure and two occupational studies have found associations with indicators of liver impairment (Lash and Parker 2001). One study found a statistically significant increase in total serum GGT among exposed workers and the second study found mild to moderate changes in the ultrasounds of liver parenchyma among exposed workers. The studies did not observe frank **liver disease** however, leading one review to conclude that there is no clear evidence of an association with non-cancer liver disease (WHO 2006).

Four studies of **kidney** biomarkers among dry cleaning workers obtained conflicting results (Ruder 2006). However, two reviews concluded that a minor effect on tubular kidney function, possibly indicative of an early stage of progressive kidney disease, could be caused by occupational PCE exposure (Lash and Parker 2001; WHO 2006). Two dry cleaning worker cohort studies found excesses in mortality due to **kidney disease** (SMR=2.33; 95% CI: 0.62-5.95; and SMR=1.4; 95% CI: 0.7-2.5 among the higher exposed) (Ruder et al. 2001; Blair et al. 2003).

An OR of 1.4 (95% CI: 0.9-2.2) was found in a case-control study linking work as a dry cleaner and **scleroderma** (Garabrant et al. 2003). However, in the same study, self-reported exposure to PCE that was confirmed by expert review was not associated with

scleroderma. No studies of PCE exposure and skin disorders were found.

Occupational and environmental studies of chronic low-level PCE exposure utilizing neurobehavioral test batteries have found impairments in **neurological function** including deficits in visual and motor function, memory, attention, vigilance and blue-yellow color perception (Oshiro et al. 2008; WHO 2006; Ruder 2006). A study of drinking water contaminated with a mixture of TCE and PCE and their degradation products utilized a neurobehavioral test battery and found deficits (p <0.10) in the digit symbol, contrast sensitivity C test, and contrast sensitivity D test and a higher mean score (p <.10) for depression (Reif et al. 2003). A strong interaction with alcohol consumption was found for some of the tests.

A recent study of offspring of dry cleaning workers found an excess of **schizophrenia** (RR=3.4, 95% CI, 1.3–9.2) based on 3 cases born to exposed fathers and 1 case born to an exposed mother (Perrin et al. 2007). In a study of PCE-contaminated drinking water in 8 Cape Cod towns, prenatal and early post-natal exposure to PCE-contaminated drinking water was not associated with **developmental disorders** of attention, learning or a diagnosis of attention deficit disorder or hyperactive disorder (Janulewicz et al. 2008).

Adverse reproductive effects have been observed among dry cleaning workers including miscarriage and longer times to pregnancy among women and spermatogenic effects in men (Ruder 2006; WHO 2006; CA 2001; Doyle et al. 1997). The strongest evidence is for miscarriage where consistent findings of increased rates have been observed. Two studies found a reduced probability of pregnancy among exposed women (WHO 2006; Sallmén et al. 1995). It is not known whether the spermatogenic effects

would affect fertility (WHO 2006).

In summary, based on the evidence from occupational and drinking water studies of PCE exposure, several diseases should be evaluated in future studies at Camp Lejeune: esophageal cancer, pancreatic cancer, lung cancer, cervical cancer, bladder cancer, kidney diseases, scleroderma, miscarriage, and infertility. Evaluation of rectal cancer, leukemia and NHL may also be warranted based on the findings in the drinking water studies.

Other VOCs

No drinking water studies have evaluated the effects of exposures to vinyl chloride, trans-1,2-dichloroethylene (DCE) or benzene on cancers or other chronic diseases. Both benzene and vinyl chloride are considered as known human carcinogens. DCE is not classifiable as to its carcinogenicity because of a lack of studies and there are no studies of DCE exposure and chronic diseases.

Occupational exposure to **vinyl chloride (VC)** is strongly associated with liver angiosarcoma. A meta-analysis of studies of VC-exposed workers and soft tissue sarcoma obtained an overall SMR of 2.52 (95% CI: 1.56-4.07) (Boffetta et al. 2003). Brain cancer mortality was also elevated based on five worker studies (SMR=1.26; 95% CI: 0.98-1.62). A more recent vinyl chloride worker study found a slight increase in lung cancer incidence in the highest cumulative exposure group (OR=1.51; 95% CI: 0.65-3.47) (Scelo et al. 2004). Vinyl chloride workers are also at increased risk for liver cirrhosis (Grosse et al. 2007).

Occupational exposure to **benzene** has been associated with acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic lymphocytic leukemia, multiple

myeloma, NHL, aplastic anemia, and miscarriage (Khan 2007; Steinmaus et al. 2008; Rinsky et al. 2002; Glass et al. 2003; Mehlman 2006; Infante 2006). The strongest evidence is for an association with AML, whereas the evidence for the other diseases is less certain due to inconsistent findings, small numbers of exposed cases, or the lack of sufficient studies (HEI 2007). Low dose, BTEX (benzene, toluene, ethylbenzene and xylenes) exposure determined by breath analyses was associated with lowered preovulatory luteinizing hormone among female U.S. Air Force personnel suggesting that these exposures may affect female reproductive function (Reutman et al. 2002).

Occupations involving exposures to **solvents** have been linked to neurodegenerative diseases although the evidence is not strong (Dick 2006). Multiple sclerosis (MS) has been linked to occupational solvent exposure in several studies (Dick 2006; Riis et al. 2002). One literature review of the relationship between occupational exposure to solvents and MS concluded that an association was possible even though these studies had various limitations (Landtblom 1997). Motor neuron disease (or amyotrophic lateral sclerosis [ALS]) has been associated with occupational solvent exposure in some studies but not others (Noonan et al. 2002; Dick 2006). In three recent studies, cohorts at two refinery/petrochemical plants had a nearly two-fold excess of ALS deaths at both plants (Huebner et al. 2004); a case-control study of usual occupation on death certificates from 22 states found a slight excess of ALS deaths (MOR=1.16) associated with solvent exposure and benzene exposure (Park et al. 2005); and a small case-control study that included 10 cases with solvent-related job titles found a slight excess of ALS (OR=1.12) but no association with job duration (Gait et al. 2003).

Occupational exposures to solvents have also been associated with adverse

reproductive outcomes among female workers. In one study, women diagnosed with infertility were more likely occupationally exposed to solvents than fertile women (Smith et al. 1997). Among the causes of infertility in these women, solvent exposure was associated with endometriosis, tubal-factor infertility and ovulatory-factor infertility. A recent study of female shoe manufacturing workers exposed to a variety of solvents found an association with reduced fertility as measured by time to pregnancy (Sallmén et al. 2008).

In summary, based on the evidence from occupational studies of benzene and other VOC exposures, several diseases should be evaluated in future studies at Camp Lejeune: liver cancer, brain cancer, leukemias, multiple myeloma, aplastic anemia, MS, ALS, infertility and endometriosis.

Summary of Literature Review on Health Effects of VOC-Contaminants

Virtually all of the epidemiologic studies of the VOC contaminants present in the drinking water at Camp Lejeune evaluated occupational exposures. There is uncertainty about the relevance of these studies to drinking water exposures. In addition, there is uncertainty as to whether the levels of drinking water contamination and the duration of drinking water exposures at Camp Lejeune were sufficient to cause adverse health problems in adult populations. A panel of epidemiologists convened by ATSDR on March 18, 2008 noted that while the average tour length for Marines is 3 years, many had shorter tours. Although the panel was not charged to evaluate the toxicity of the contaminants and did not reach consensus on whether the levels and duration of exposures were sufficient to cause diseases in an adult population, the panel recommended that future studies of mortality, cancer incidence, and non-cancer diseases

were worth conducting at Camp Lejeune.

The literature review has identified several cancers and other diseases that should

be evaluated in future studies. These include:

- aplastic anemia (benzene)
- bladder cancer (PCE)
- brain cancer (VC)
- breast cancer (PCE)
- cervical cancer (TCE, PCE)
- endometriosis (solvents)
- esophageal cancer (PCE)
- generalized skin disorders (TCE)
- Hodgkin's disease (TCE)
- infertility (PCE, TCE, solvents)
- kidney cancers (TCE)
- kidney diseases (TCE, PCE)
- leukemias (TCE, benzene, PCE)
- liver cancer and liver disease (TCE, VC)
- lung cancer (PCE, VC)
- lupus (TCE)
- motor neuron disease/ALS (solvents)
- multiple myeloma (TCE, benzene)
- multiple sclerosis (solvents)
- NHL (TCE, PCE, benzene)
- pancreatic cancer (PCE)
- Parkinson's disease (TCE)
- scleroderma (TCE, PCE)
- soft tissue sarcoma (VC)
- miscarriage (PCE, benzene)

LITERATURE REVIEW ON SURVEY METHODS

A key source of bias in survey research is non-response. A 1997 review of 321 mail

surveys published in medical journals in 1991 estimated an average response rate of about

60%, with surveys of physicians and "non-physicians" having average rates of 54% and

68% respectively (Asch et al. 1997). A more recent review of 13 health surveys estimated

an average response rate of 65% (Nakash et al. 2006). Another review of health surveys

concluded that a 60% response rate when surveying the general population is standard for

"acceptability" – although achieving this standard requires considerable effort and resources

associated with precontact, incentives, or reminder postcards or calls (Rosoff et al. 2005).

Several mailed surveys have been conducted of military personnel. The median response rate for Gulf War related survey research is about 65% (Hotopf and Wessely 2005). A mailed survey of pregnancy outcomes among Gulf War veterans achieved a 70% response rate (Kang et al. 2001). However, a mailed survey of Navy active duty women with a 1993 pregnancy that evaluated occupational and environmental exposures and adverse pregnancy outcomes achieved only a 56% response rate among those who were reached by the mailing (Hourani and Hilton 2000). Finally, the mailed survey of the Millenium Cohort (256,400 sampled from U.S. military personnel) achieved a response rate of about 36% (Ryan et al. 2007).

Several strategies have been identified to minimize nonresponse bias and increase response rates. These strategies include: a concise questionnaire, personalized letters, pre-notice letters, intensive mail and telephone follow-up, stamped return envelopes, sponsorship/endorsements, monetary incentives or reimbursement for time and effort, and a hybrid data submission system (hardcopy and web-based) (Asch et al. 1997; Dillman 2007; Edwards et al. 2002; Edwards et al. 2007; Larson and Chow 2003; Eaker et al. 1998; Schonlau et al. 2003; Smith et al. 2007; Hayslett and Wildemuth 2004; Kongsved et al. 2007; Nakash et al. 2006). In addition, researchers involved in the Millennium Cohort Study have found that informational web pages, including useful links and study contact information, and signed endorsements from leaders in the military community were important components in establishing a personal relationship with participants and emphasizing the legitimacy and need for the study (Smith et al. 2007).

Survey researchers follow the set of techniques described in the Dillman Total

Design Method in order to increase response rates in mail surveys (Dillman 2007). These

techniques include using a set of timed mailings that are personalized in appearance and

tone in order to invoke a participant's sense of the importance of his or her contribution

towards the research effort (Filip et al. 2004). Reviews of mail survey strategies to increase

response rates have found that increased numbers of contacts with potential respondents

result in increases in response rates (Kaplowitz et al. 2004). The conduction of several

follow-up mailings also allows for assessment of nonresponse bias by comparing responses

to particular questions by early responders versus late responders (Larson and Chow 2003).

The first step in the Dillman Total Design Method, the mailing of a brief pre-notice

letter shortly before sending the questionnaire, appears to have the strongest effect on

response rate (Kaplowitz et al. 2004). The pre-notice letter notifies the potential respondent

that a questionnaire for an important survey will arrive in a few days and that the person's

response would be greatly appreciated (Dillman 2007). For a survey of a military cohort,

the pre-notice should be signed by the highest ranking officer of the military branch (or

branches) being surveyed and it may also be efficacious to include endorsements by other

leaders in the military community (Smith et al. 2007).

According to the Dillman Total Design Method, the questionnaire mailing should

include a detailed cover letter explaining the significance of the study and why a response is

important (Dillman 2007). Sending the questionnaire by certified mail has been shown to

increase the response rate (Edwards et al. 2002). A "thank you postcard" is sent about a

week after the questionnaire mailing, expressing appreciation for responding and

encouraging a response if the completed questionnaire has not yet been returned (Dillman

2007). If no response is received, then a replacement questionnaire is sent to the

nonrespondent with a letter urging a response (Dillman 2007). Additional reminder

mailings and a telephone contact have been shown to increase response rates by 10% to

30% (Nakash et al. 2006; Asch et al. 1997; Converse et al. 2008). In one study, the use of

telephone reminders appeared to be less effective than postcard reminders send by certified

mail but more effective than normal delivery postal reminders (Nakash et al. 2006).

However, response rates have been shown to improve if both mailed and telephone

reminders are conducted (Filip et al. 2004)

The saliency of a questionnaire has been shown to be one of the strongest predictors

of response (Nakash et al. 2006). A salient questionnaire would address issues that are

current and of importance to the targeted population. To improve saliency, the more

relevant questions are placed first and more general questions are placed later in the

questionnaire (Edwards et al. 2007). Shortening the questionnaire can improve response

rates, but a longer questionnaire may be necessary to in order to address the research topic.

This trade-off between conciseness and comprehensiveness can be evaluated by pretesting

the questionnaire to achieve the optimum length that will address the research need

(Hayslett and Wildemuth 2004).

There is uncertainty about the effectiveness of monetary incentives. In a recent

review of 69 surveys, the odds of response were almost doubled using monetary incentives,

but there was significant heterogeneity of response effect across these surveys. The odds of

response were two-thirds higher when incentives were sent with the questionnaire and were

not conditional on response (Edwards et al. 2007). An earlier review of surveys found

similar results – an increase in response when monetary incentives were given not

conditional on response (Edwards et al. 2002). Conversely, a review of 13 mail health

surveys found no evidence that incentives improved response rates (Nakash et al. 2006).

One review concluded that if the researchers have a limited budget, then intensive follow-up

is preferred over monetary incentives, but monetary incentives would be effective if the

researchers face significant time constraints (Larson and Chow 2003). It is unknown

whether retired military personnel would respond in a similar fashion as the general

population to monetary incentives.

Providing respondents with a choice as to how to participate (hardcopy or web-

based) appeals to those who may be concerned about privacy on the Internet and to those

concerned about sending personal information by US mail (Smith et al. 2007). Potential

benefits associated with Web-based surveys include reduced costs, faster responses,

automated data collection, and electronic skip patterns and range checks (Converse et al.

2008; Ryan et al. 2007; Fleming et al. 2007; Smith et al. 2007). The key disadvantage

associated with web-based surveys is that response rates have tended to be much lower

than for mail surveys (Converse et al. 2008). However, a meta-analysis of web and mail

surveys found that when respondents were offered both a mail survey and a web survey

at the same time, response rates were not significantly different (Shih and Fan 2007). In

the Millenium Cohort survey, more than half of the respondents chose to complete the

web survey (Smith et al. 2007).

One of the key problems identified in the surveys of Gulf War veterans is the

difficulty tracing those who left military service (Hotopf and Wessely 2005). For

example, addresses in the personnel database at the Defense Manpower Data Center

(DMDC) were often found to be inaccurate or incomplete (Doebbeling et al. 2002). One

survey achieved an overall location rate of 84% of sampled subjects by conducting a

multi-phased locating process that included the mailing of a pre-notice letter with forwarding services requested and the utilization of commercial tracking firms (Doebbeling et al. 2002).

PROCEDURES

Morbidity Study Design

The morbidity study population consists of those identified by the DMDC personnel databases or the 1999-2002 ATSDR survey as having lived or worked at Camp Lejeune during the period of drinking water contamination and a comparison population of active duty personnel and civilian employees sampled from Camp Pendleton. The morbidity study will evaluate the relationships between specific diseases of interest and exposure to drinking water contaminated with TCE, PCE, other chlorinated compounds, and/or BTEX compounds (i.e., benzene, toluene, ethyl benzene, and xylenes). These specific diseases of interest were selected based on a literature review of occupational and drinking water studies involving solvent exposure and include aplastic anemia, bladder cancer, brain cancer, breast cancer, cervical cancer, endometriosis, esophageal cancer, generalized skin disorders, Hodgkin's disease, infertility, kidney cancers, kidney diseases, leukemias, liver cancer, liver disease, lung cancer, lupus, motor neuron disease/ALS, multiple myeloma, multiple sclerosis, NHL, pancreatic cancer, Parkinson's disease, scleroderma, soft tissue sarcoma, and miscarriage.

This retrospective cohort morbidity study will utilize a health survey to identify the cancers and other diseases as well to obtain information on potential confounders such as smoking, alcohol consumption, and occupational exposures. Information on the self-reported conditions obtained from the survey will include the type of condition, age at

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diagnosis, state of diagnosis, and contact information for the health provider who

provided the diagnosis. Except for miscarriage, only diseases confirmed by medical

records, death certificates or cancer registrations will be evaluated in the primary

analyses. Self-reports of miscarriages will be considered "confirmed" if the respondent

answers affirmatively that a positive pregnancy test was conducted before the miscarriage

occurred **and** that the miscarriage was confirmed by a health provider (Axelsson 1990).

The exposure assessment will be based on groundwater contaminants fate and

transport and water distribution system models for the Hadnot Point, Holcomb

Boulevard, and Tarawa Terrace drinking water systems. These models will provide

historical monthly average levels (and Monte Carlo 95% interval ranges) of contaminants

in the drinking water distribution systems serving family housing and bachelor quarters

on base from the period when these drinking water systems came on line until

contaminated wells in the Hadnot Point and Tarawa Terrace systems were shut down.

<u>Enrollment of Study Participants</u>

One to two weeks before the survey is mailed (Appendix 1), a pre-notice letter

will be mailed (Appendix 2), signed by the highest ranking officer of the USMC,

informing potential respondents that they will shortly receive a questionnaire in the mail

and encouraging their participation. If a study participant is known to be deceased, the

survey will be mailed to the next of kin if the name and address are available. To

determine those in the study population who have died, name, date of birth, and SSN will

be matched with the Department of Veterans Affairs Beneficiary Identification Records

Locator System (VA BIRLS), the Social Security Administration (SSA) Death Master

File, the Medicare Vital Status File, and the National Death Index (NDI), and the death

certificate from the health department in the state where the death occurred will be requested. Information provided by the USMC as part of its notification process will also be used to identify those who have died as well as next-of-kin. The information on the deceased person's health conditions and risk factors will be included in the morbidity study only if a completed health survey is received from the next-of-kin.

Data Collection

To determine the optimum length of the survey instrument that still answers the research questions of interest, the survey has been pilot tested on five volunteers. The findings of this pilot testing were that the average length of time to complete the survey was 45 minutes and that some of the skip patterns needed to be changed.

Using Dillman's Tailored Design Method (Dillman 2007), participants will be mailed a personalized pre-notice letter signed by the highest ranking officer of the USMC explaining that a survey would be arriving soon and encouraging participation. A personalized letter of invitation (Appendix 2), hardcopy survey, and a preaddressed stamped return envelope will be mailed one to two weeks after the pre-notice letter; the letter of invitation will also direct participants to a web-based version of the survey if they prefer to answer on-line. An e-mail invitation (Appendix 2) will also be sent when an e-mail address is available. Within two weeks, a postcard reminder/thank you (Appendix 2) will be sent via US mail to all participants as well as an email reminder/thank you (Appendix 2) if possible. A second survey mailed with a letter (Appendix 2) similar to the initial survey mailing and a second email reminder (Appendix 2) if possible will be sent to those participants who have not responded within four weeks after receiving the postcard reminder. If a respondent does not wish to participate, the second survey package will

include a stamped postcard with suggested choices for the reason for non-response to obtain additional information that could be used to assess the likelihood of selection bias. Telephone reminders (Appendix 2) will also be conducted if participants have not responded to the survey within two weeks after the second mailing.   In an attempt to minimize information bias as much as possible, the letter of invitation, e-mail invitation, and consent form will not specifically mention the contaminated drinking water. Instead, these communications will inform respondents that ATSDR is conducting this research activity to learn more about the health effects of workplace and environmental exposure to chemicals.

Informed consent, either hardcopy or electronic, will be obtained from the participants (Appendix 3). The health survey will collect information on the following diseases an individual may have had that was diagnosed by a health provider: any cancer, Parkinson's disease, kidney failure and other severe kidney diseases, severe liver diseases, lupus, aplastic anemia, TCE-related skin disorders, scleroderma, multiple sclerosis, motor neuron disease/amyotrophic lateral sclerosis (ALS), infertility, endometriosis and miscarriages. Requested information for cancers will include the type of cancer, date of diagnosis, and state of diagnosis to facilitate the acquisition of cancer registry data. Because medical records are usually unavailable for miscarriages, the survey will not request information to facilitate medical record confirmation of this adverse outcome. Instead, the survey will include two questions ("Did you have a positive pregnancy test before the miscarriage occurred?" and "Was the miscarriage confirmed by a physician or other health provider?") that have been shown to improve the accuracy of self-reported miscarriages (Axelsson 1990). If the respondent answers affirmatively to both questions, then the miscarriage will be considered "confirmed". Self-reported cancers and other diseases will

be confirmed by medical records or cancer registrations if ATSDR decides to complete the study (see Expert Panel section). To facilitate medical record confirmation, the participant will be asked to provide a copy of the medical record to ATSDR or to sign a medical records release form allowing ATSDR to gain access to the medical record. However, if the identified medical provider requests their own Health Insurance Portability and Accountability Act (HIPAA) compliant form be used, we will follow up with the participant and ask them to sign the additional form as well. The survey will also include a space so that the respondent can report other disease conditions not specifically mentioned in the questionnaire. These self-reported conditions will not be confirmed and will be evaluated only in a descriptive manner (e.g., a frequency table on self-reported "other conditions").

ATSDR is attempting to gain the cooperation of all 50 state cancer registries as well as the DOD and the VA registries to assist in confirming the self-reported cases of cancers. Cancers confirmed using cancer registry data will be classified into cancer site groups (e.g., the cancer site groups in Table A-5 of the SEER Cancer Statistics Review, 1975-2003) using the subjects' International Classification of Diseases for Oncology (ICDO) ICDO-1, ICDO-2, or ICDO-3 topology and morphology codes. Cancers confirmed by medical records will also be classified in a similar manner to cancer site groups using the information in the record.

The survey will also collect information on residential history on base, occupational history, and information on several risk factors (e.g., socio-economic status, demographics, smoking, alcohol consumption, etc). The collected information will be used as a basis to assign exposure status and to assess potential confounding.

Non-response (Selection) Bias

Even though intensive methods will be used to increase participation rates and convert non-responders, non-response (or selection) biases are still a concern. To partly address the issue of selection or non-response biases, the morbidity study will: 1) include only those identified a priori from the DMDC personnel databases and the ATSDR 1999-2002 survey; 2) use Dillman's Tailored Design Method for mailed surveys; and 3) include in the mailings a letter signed by the highest ranking USMC officer encouraging participation in the study. However, even a high participation rate will not be sufficient to rule out possible biases due to non-response. Therefore, sensitivity analyses will be conducted to assess the likelihood and magnitude of potential selection (or non-response) biases.

Initially, the sensitivity analyses will compare those who participate and those who do not on variables available from the personnel databases and family housing databases to identify risk factors associated with response. Next, participation rates will be stratified by several factors including exposure grouping (Camp Lejeune exposed, Camp Lejeune unexposed, Camp Pendleton), a categorical variable for duration of exposure, rank/pay grade (e.g., officer vs. enlisted), by subgroup-Marine base stratum (marines/civilian employees/dependents at Camp Lejeune; marines/civilian employees at Camp Pendleton), and other demographics (e.g., age, race/ethnicity, sex, education level). Participation rate will be defined as the number of completed surveys divided by the total number of sampled individuals for whom current address is available. Logistic regression analyses will also be conducted to identify predictors of response/non-response and early/late response (Steffen et al. 2008).

Expert Panel

An expert panel of four to six scientists with extensive expertise in epidemiological studies of cohorts and/or health survey research involving mailed surveys will be assembled by the contractor and will meet quarterly until the study is completed. ATSDR, the USMC/Department of Navy (DON), and the ATSDR Camp Lejeune Community Assistance Panel (CAP) will nominate candidates for the expert panel. Panel members must have no financial conflict of interest.

The panel will evaluate the ongoing progress of the first phase of the morbidity study – the mailing of the health surveys and the resulting participation rates for the cohorts. The panel will also consider the power calculations and evaluate the results of the sensitivity analyses. Based on the power calculations, the progress of the first phase and the sensitivity analyses, the panel will make recommendations concerning whether to confirm self-reported diseases from the survey. ATSDR will take in to account the panel's recommendations in determining how to proceed with the completion of the study. The first phase will continue until all efforts to increase participation (including phone contact reminders) are exhausted, as specified in the Data Collection section.

It is likely that no single piece of evidence or specific analysis will be sufficient to provide the basis for the panel's recommendations. For example, selection bias in the morbidity study is possible even with a high participation rate ($\geq$65%), while a low participation rate may have minimal selection bias (Groves 2006; Galea and Tracy 2007). Moreover, published mail survey studies have widely varying response rates which are likely due to differences in population surveyed and by survey administration methods. In the early 1990s, a 60% response rate for mail surveys was suggested as a "standard for

acceptability" (Evans et al. 2004). One review of 13 mailed health surveys conducted

prior to 2005 estimated an average response rate of 65% (Rosoff et al. 2005; Nakash et al.

2006). A recent meta-analysis of 39 mailed surveys obtained an average response rate of

45% with a range of response rates of 10% to 89% (Shih and Fan 2008). Given that recent

mailed health surveys of military populations have achieved response rates of between 30%

and 40% (Kang et al. 2009; Ryan et al. 2007), a realistic goal for the study may be to

achieve a participation rate of at least 40%.

Exposure Assessment

Owing to the paucity of historical, contaminant-specific data, the exposure

assessment will consist of an historical reconstruction of the spatial and temporal

distribution of the contaminant-specific compounds at locations (such as residences or

worksites) serviced by a water distribution system using ground water fate and transport and

distribution system models. This historical reconstruction modeling is being conducted for

the study "Exposure to Volatile Organic Compounds in Drinking Water and Specific Birth

Defects and Childhood Cancers at United States Marine Corps Base Camp Lejeune, North

Carolina". The modeling will provide monthly average estimates (and monthly Monte

Carlo simulated 95% interval ranges) of the concentrations of contaminant-specific

compounds in drinking water delivered to study subject residences or worksites.

Information collected in the survey, as well as information on the areas and family housing

units served by each drinking water system, the locations where units were barracked,

family housing records, and location of worksites will be used to assign exposures.

The primary exposure assessment will be based on the contaminant levels in the

drinking water serving the person's residence (or workplace location for civilian

employees). Each month of residence (or civilian employee's workplace) will be linked to the estimated levels of contaminants in the drinking water serving that location for that month. The person's cumulative exposure will be calculated as well as the average exposure, maximum level of exposure, and exposure duration. These exposure metrics will also be categorized *a priori* into meaningful categories (based on the contaminant level distribution) as well as categorized using a smoothing technique (e.g., LOESS and/or splines). Other possible exposures (i.e., to contaminated drinking water in field training, at the work location of the active duty personnel, or occupational exposures to solvents during the active duty individual's work service) will be explored if sufficient information is obtained from the health survey instrument and personnel databases to assess these exposures.

The military occupation specialty (MOS) code for active duty personnel and the occupation code for civilian employees will be obtained from the DMDC data. Based on discussions with knowledgeable former Marines and current occupational hygiene employees at Camp Lejeune, ATSDR obtained information on the types of chemicals used in various military and civilian occupations at the base. The MOS and civilian occupation codes will be linked to this information to assess potential occupational exposures to chemicals at the workplace.

The locations of workplaces (and the water system serving these locations) will be based on discussions with knowledgeable former Marines and current staff at Camp Lejeune as well as on survey information provided by the respondent. Drinking water in the field was provided in tanks and "buffaloes"; the water could have come from anywhere on base, but most likely came from Hadnot Point. For this reason, it was deemed possible that all

active duty personnel were exposed to contaminated drinking water at Camp Lejeune during their field training and this will be addressed in the data analysis.

Determining the water quality at residences and workplaces at Camp Lejeune is simplified by the fact that, within each water system, the water was completely mixed so all locations served by a water system received similar levels of contamination. It is therefore only necessary to determine in which broad area of the base the residence or workplace is located. The information from the family housing records (for married active duty personnel), the unit identification codes (for single active duty personnel), the MOS code (for active duty workplaces), and the occupation code (for civilian employees), when combined with the information obtained from command chronologies, discussions with knowledgeable former Marines and current base staff, and survey information provided by the respondent, should be sufficient to identify the area of the base where a residence or workplace was located and to determine which water system served that residence or workplace.

Because of uncertainties and variabilities concerning the amount of water each individual routinely consumed (i.e., by ingestion, inhalation and dermal routes), the source of water in the field, the amount of time an individual routinely spent outside the base or in other parts of the base besides the residence, exposure misclassification bias is likely. This bias should be non-differential, i.e., not associated with disease status. However, non-differential exposure misclassification can distort exposure-response relationships. One approach to reduce the effects of this bias on the exposure-disease relationship is to compare the group with the most certainty of being the highest exposed to the unexposed group. To assess the possible impact of this bias, sensitivity analyses will be conducted assuming

different values for the sensitivity and specificity of the exposure classification.

<u>Morbidity Study Population</u>

Persons eligible for the morbidity study are those with accurate and complete addresses
who were:

1. Marines and Navy personnel identified from the DMDC computerized
   personnel database as having been stationed at Camp Lejeune anytime during
   the period June 1975- December 1985;

2. civilians identified from the DMDC computerized personnel database as
   having worked at Camp Lejeune anytime during the period December 1972 to
   December 1985;

3. respondents and their children (who were born prior to 1986 and who are now
   adults) included in the 1999-2002 ATSDR survey;

4. Marines stationed at Camp Pendleton anytime during the period June 1975-
   December 1985, but who were not at Camp Lejeune anytime during the
   period of drinking water contamination; and

5. civilians employed at Camp Pendleton anytime during the period December
   1972-December 1985 who were not at Camp Lejeune anytime during the
   period of drinking water contamination.

The study population is defined based on available data indicating at which base
the person was stationed or employed. The DMDC personnel records for active duty
Marines and Navy personnel do not have information on where the person was stationed
(i.e., the unit code) until June 1975. Therefore, the period, June 1975-December 1985
was chosen for inclusion of active duty personnel. The DMDC personnel records for

civilian employees began in December 1972 so the period, December 1972-December 1985 was chosen for civilian employees. There is overlap between Marines and Navy personnel included in the DMDC active duty database and the ATSDR 1999-2002 survey; about 65% of the active duty personnel included in the ATSDR survey are also in the DMDC database.

The Camp Lejeune Community Assistance Panel, as well as the panel of epidemiologists convened by ATSDR in 2008, recommended that an unexposed comparison group similar to the Camp Lejeune population be included in order to enhance the scientific credibility of the study. Camp Pendleton was chosen for the comparison population because the base is similar to Camp Lejeune. Camp Pendleton primarily provides training for Marines residing west of the Mississippi while Camp Lejeune primarily provides training for Marines residing east of the Mississippi, although some Marines receive training at both bases. Camp Pendleton has toxic waste sites just like Camp Lejeune. Additionally, the available personnel records are similar for both bases. The major difference is that Camp Pendleton did not have a contaminated drinking water supply.

Current addresses (and if necessary, current names) for the study population will be obtained using a locator firm. The DMDC data includes name, date of birth and social security number. Most of the respondents to the ATSDR 1999-2002 survey provided their social security numbers, and dates of birth are available for both parents and the study child. Although pregnant women and prisoners are not specifically targeted under this data collection, they will not be excluded.

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 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. Table 1 provides estimates of the minimum meaningful effect size (i.e., the incidence rate ratio or "RR") for various cancers assuming an alpha error of 0.10 (i.e., equivalent to using a 90% confidence interval), a beta error of 0.10 (i.e., 90% statistical power), and various estimates of exposure prevalence in the surveyed population. The expected number of cancers provided in Table 1 are based on the age-specific 1999-2004 U.S. cancer incidence rates (all genders and race/ethnicity groups combined) from the National Program of Cancer Registries and estimates of the person-time contributed to each 5-year age grouping by the surveyed population after a 10-year lag to account for a latency period. The table assumes that the survey is sent to 247,000 from Camp Lejeune and 60,000 from Camp Pendleton and that the overall response rate for the survey is 65%. For most cancers, the minimum detectable RR is less than 2.0.

Reimbursement

No remuneration will be offered to participants.

Human Subjects and Confidentiality

The Centers for Disease Control and Prevention (CDC) and ATSDR Privacy Act Officer has reviewed this Institutional Review Board (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 (date of birth, social security number) must be verified or obtained in order to conduct the study and analyze

the data. Privacy Act clauses will be included in the contract to protect against

inappropriate data disclosures. 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. Computerized data analysis files will contain identification numbers

only.

To access the web-based survey, participants will receive a personal identification

number (PIN) to be used for authentication to ensure that only the study population can

participate in the survey and that the survey is not completed more than once by the same

participant. Data collected over the internet will be transmitted in an encrypted format to

ensure that any data intercepted during transmission cannot be decoded; data will also be

stored in an encrypted format on password-controlled servers to protect personally

identifiable information.

The study is performed 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 about cancers and other diseases may be sensitive to some persons, but are not more than minimal risk. The questionnaire will be reviewed and approved by the CDC/ATSDR IRB prior to being administered to participants.

All respondents will be informed that providing the requested information is entirely voluntary and informed consent will be obtained. Those participants who complete the survey on-line will be informed that they can print out a copy of the consent form for their records. Additionally, they will be told that by clicking the "I agree" button on the computer screen, they are agreeing to take part in the survey. 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. The waiver is only requested for participants who complete the web-based survey. The web-based survey takes approximately 45 minutes and participants must click the "I agree" button before beginning the survey. We are also requesting a waiver of the prisoner regulations since the research does not fit into the research categories specified in 45 CFR46.306. This waiver allows inclusion of prisoners in epidemiological

research if (1) the epidemiologic study's sole purposes are "to describe the prevalence or incidence of a disease by identifying all cases, or to study potential risk factor associations for a disease"; (2) the study poses no more than a minimal risk and no more than an inconvenience to the prisoner; and (3) "prisoners are not a particular focus of the research." This study meets all of these criteria: 1) the study's purpose is to describe the prevalence and risk factors for health problems related to exposure to TCE contaminated water at the Camp Lejeune military base, 2) the study poses no more than minimal risk and participation would be no more that an inconvenience to the prisoner, and 3) the focus of the research is not prisoners, but people formerly stationed at or employed by the Camp Lejeune marine base.

 Quality Control

All electronically entered information obtained from surveys will be reviewed for missing data and ambiguous responses. Internal consistency and validity programs will be used to identify and correct coding and data entry errors. The web-based survey will include prompts to alert participants if they incorrectly answer or skip questions; drop down boxes that present ranges of possible answers; and electronic skip patterns that automatically skip irrelevant questions.

Data Analysis

The civilian employees will be analyzed separately from the active duty personnel and their dependents. This is because the primary exposure to drinking water contaminants for the civilian employees is not the residence, but the workplace location. If the exposure-response relationship for a specific condition in the analysis of civilian employees is observed to be similar to that observed in the analysis of active duty

personnel and their dependents, then a combined analysis may be conducted.

In the analysis of active duty personnel and their dependents, there are no dependents from Camp Pendleton. It will be assumed that dependents and active duty personnel with similar residential drinking water exposures (including no exposure) will have similar risks for a condition. In subsequent analyses, effect modification of the exposure-response relationship for a specific condition by whether the respondent was a dependent or active duty personnel will be explored.

Person-time will accumulate from the date the person first resided or worked at Camp Lejeune (or Camp Pendleton) until date of death or the date that the health surveys are mailed. The monthly average levels of contaminants in the drinking water will be used to estimate exposure. The exposure intensity (average and maximum exposure level), exposure duration, and cumulative exposure measures will be calculated. In addition, these exposure measures will be categorized using a priori meaningful cutpoints and/or quantiles based on the exposure distribution of respondents from Camp Lejeune, and cutpoints from a smoothing procedure (e.g., splines or LOESS). The monthly Monte Carlo 95% interval range for each contaminant will be taken into account during the categorization of exposure variables.

The analyses will focus on reported diseases of interest that are confirmed by medical record, death certificate, or cancer registration. However, because medical records are generally unavailable for miscarriages, a miscarriage will be considered "confirmed" if affirmative responses are provided to two survey questions: "Did you have a positive pregnancy test before the miscarriage occurred?" and "Was the miscarriage confirmed by a physician or other health provider?" These two questions have been found

to improve the accuracy of self-reports of miscarriages (Axelsson 1990).

Poisson regression methods will be used to evaluate exposure-disease relationships, with exposure measures and potential confounding factors included in the models as independent variables. Logistic regression may be used to check the Poisson regression results. Survival analysis methods with age as the time variable may also be used to evaluate relationships between disease and continuous exposure (and confounder) variables. Exposure will be lagged to account for an appropriate latency period for each condition. For most cancers, the initial analyses will lag exposure by 10 years (i.e., a 10-year latency period). Additional analyses will explore other latency periods for each condition. Selection of risk factors for inclusion in the models as confounders will be based on a "10% change in the estimate" rule (Maldonado and Greenland 1993). Models will also be constructed that include well-known risk factors for the disease under evaluation from information obtained in the survey. Ninety percent confidence intervals will be calculated for parameter estimates.

The first confirmed diagnosis of a generalized skin disorder will be used in the analysis. For miscarriage, two approaches will be used. First, we will evaluate only the first pregnancy that occurs at the base. Second, we will include all pregnancies that occur in the follow-up period and employ the generalized estimating equation (GEE) approach to account for non-independent outcomes arising from multiple pregnancies for the same woman. Induced abortions and ectopic pregnancies will be excluded from the analyses of miscarriage. For the GEE analyses, the logit link will be employed and the correlation

structure will assume equal correlation between birth outcomes for the same woman.

All comparisons will be "internal comparisons" where the Camp Pendleton cohorts will be the unexposed group. If those at Camp Lejeune whose residences were not served by contaminated water have a similar risk for a specific disease as the Camp Pendleton cohorts, then they will be included along with the Camp Pendleton cohorts in the unexposed group. If their risks are observed to be different, then an indicator variable will be included in the analyses that distinguishes the unexposed at Camp Lejeune from the unexposed at Camp Pendleton.

Since drinking water in the field was provided in tanks and "buffaloes" that could have come from anywhere on base, but most likely came from Hadnot Point, it was deemed possible that all active duty personnel were exposed to contaminated drinking water at Camp Lejeune during their field training. This is the primary reason why unexposed comparison groups from Camp Pendleton are necessary. In the subsequent analyses, it will be assumed that all active duty Marines had the potential for drinking water exposures in the field. A variable for field drinking water exposure (based on the contamination levels at Hadnot Point during the period when the individual was stationed at the base) will be added to the Poisson (or Cox) regression models.

<u>Sensitivity Analyses of Selection and Information Biases</u>

For selection bias (or non-response bias) to be present, participation rates must vary jointly by exposure and disease status. Since disease information is not available for non-respondents, the likelihood and magnitude of selection bias cannot be addressed directly. One indirect approach to assess the likelihood and magnitude of selection bias is to compare exposure-disease association measures (i.e., rate ratios and exposure-

response trends) for specific, <u>confirmed</u> cancers in the morbidity study with the preliminary results for those cancers in the mortality study of former marines and civilians potentially exposed at Camp Lejeune. Cancers which are not known or suspected of being associated with the drinking water exposures (e.g., colon/rectal, prostate, stomach, and melanoma) will be evaluated. If for several cancers, substantial discrepancies that are not biologically plausible are found between the results of the mortality study and the morbidity study (e.g., for a specific cancer, the mortality study has an SMR close to 100 but the morbidity study has an RR greater than 2.0), then this may be evidence of bias in the morbidity study. However, in addition to selection bias, disease information bias, in particular, under-reporting of diseases by the Camp Pendleton comparison population, could produce discrepancies between the morbidity study and mortality study results. Although substantial under-reporting is not expected for cancers, under-reporting in the Camp Pendleton sample will be evaluated by comparing the incidence of reported, confirmed specific cancers in the Camp Pendleton sample with incidence rates from the Surveillance, Epidemiology and End Results (SEER) program and from a cancer incidence study of veterans (Harris et al. 1989). Underreporting by the Camp Lejeune respondents will be assessed in the same manner.

A second approach to evaluate the impact of potential selection bias will be to conduct sensitivity analyses to determine what level of bias would have to be present to explain differences between groups. For diseases having elevated rate ratios (e.g., RRs > 2.0), we will determine the amount of selection bias that would be necessary to produce the observed RRs if the true RR =1 using several different scenarios with the following assumptions:

- Responders have a higher disease rate than non-responders regardless of exposure status (Tao et al. 2007)

- Exposed responders have a higher disease rate than exposed non-responders, Camp Pendleton responders, or Camp Pendleton non-responders

Confirming diagnoses will minimize information bias due to over-reporting of conditions. However, confirmation may not be possible for all reported conditions of interest. To assess the extent of information bias due to inability to confirm diagnoses, the percentages of (1) medical record confirmation, (2) medical record disconfirmation, and (3) no available medical record, will be compared between the unexposed and exposed groups for the diseases of interest. In addition, sensitivity analyses will be conducted that include diagnoses for which no confirmation was possible as well as confirmed diagnoses to determine if inclusion of the non-confirmed diagnoses modifies exposure-response relationships. To minimize bias due to underreporting of conditions, (e.g., a problem that might occur among the Camp Pendleton cohorts), the pre-notice letter and the letter accompanying the health survey questionnaire will avoid mentioning the hypotheses under investigation and will not indicate who is considered exposed or unexposed.

Interpretation and Dissemination of Results

ATSDR will publish a final report of the study which will be distributed to the general public by posting it on the ATSDR Camp Lejeune website. Additionally, a presentation will be made to the USMC, the (DON, and the CAP. ATSDR will also publish the results in a peer-reviewed scientific journal. Only aggregate data presented in

tables and graphs will be published and presented.

Study participants will be mailed a summary of the final report. 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.

In order to keep respondents informed of the latest developments at Camp Lejeune concerning the drinking water contamination and health issues, ATSDR will share with the USMC updated current addresses obtained as part of the health survey mailings; the USMC already has the names and contact information of the study participants and no other information will be provided to the USMC. The USMC is required by Congress to notify former residents and employees who were at Camp Lejeune during the period of water contamination about the results of studies and other pertinent public health information. The USMC will follow appropriate measures to maintain the confidentiality of the contact information.

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, ATSDR will engage its public communications staff to assist the Camp Lejeune researchers in communicating the results of the studies. Study participants will be informed of how ATSDR measured associations and the criteria used to interpret the meanings of the associations. Specifically, ATSDR will calculate incidence rate ratios and 90% confidence intervals for each exposure-disease relationship. Incidence rate ratios (RRs) compare the disease rates among various levels of exposed to the disease rate among the unexposed adjusting for confounders. Exposure-response relationships are examined by determining whether the RRs increase with increasing exposure level. If the disease rates are the same in the exposed and unexposed groups, then the RR is equal to or close to 1.0. A RR close to or equal to 1.0 indicates that there is a lack of association between the exposure and the disease in the data. If the exposed group has a higher disease rate than the unexposed (i.e., RR is greater than 1) or if there is a trend of increasing disease rate with increasing exposure, then there is an association between exposure and disease in the data. A confidence interval provides information on the precision of the RR. The width of the confidence interval reflects the amount of variability in the RR. The wider the confidence interval, the less precise and more uncertain is the estimate of the RR. The interpretation of each exposure-disease relationship will take into account the following:

- the strength of the association (the magnitude of the incidence rate ratio or RR),

- dose-response effect (as concentration of TCE/PCE/benzene and/or the

amount of water consumed increases, so does the risk of having a cancer or other disease),

- temporality (with consideration of an appropriate latency period),
- the consistency of findings, both within the study and when compared to other epidemiologic studies, and
- biological plausibility.

In addition, the interpretation of each exposure-disease relationship will take into account the results of the sensitivity analyses of potential biases (e.g., non-response bias, disease reporting biases, and exposure misclassification). "Sub-group" analyses (e.g., examining different exposure metrics and exposure lag periods, evaluating major sub-groupings of a disease such as leukemia, and estimation of effect modification between exposure and another factor) will be conducted in order to provide supplemental information on the exposure-disease relationship. The relationship between each exposure of interest (i.e., residential drinking water exposure to a particular VOC) and each disease of interest listed in the procedures will be evaluated as a separate, *a priori*, hypothesis. Each of these hypotheses has scientific interest in its own right and will be qualitatively different from each of the other hypotheses on characteristics such as the target organ, the biological mechanism of effect, the dose-response relationship, the effect of latency, the effect of possible confounders, and the strength of the prior evidence in the scientific literature for a causal association.

ATSDR will ensure that the affected community is given information at an appropriate educational level. ATSDR will also emphasize that the ATSDR morbidity study cannot by itself establish a causal link between population exposures at Camp

Lejeune and specific diseases in an individual. The affected community will be informed

that the purpose of ATSDR's research is to contribute to our understanding of the human

health effects related to exposures such as VOCs in drinking water. The study results

will add information to the overall weight-of-evidence about human health outcomes and

exposures to TCE, PCE, benzene and other solvents found in the contaminated drinking

water at Camp Lejeune.

ATSDR will also set appropriate expectation for the morbidity study. ATSDR

cannot guarantee that the morbidity study will find positive associations or that it will

provide answers to all of the community's questions. ATSDR will acknowledge that the

observation of an association doesn't mean that there is a cause and effect relationship.

ATSDR will also acknowledge that the absence of an observed association does not

exclude the possibility of an association existing.

The limitations of the morbidity study will be appropriately communicated. The

limitations are due to uncertainties related to exposure assessment and potential study

biases (i.e., non-response bias, information bias, and inadequate control of confounders).

DISCUSSION

This is one of only a few studies to examine the associations between cancers and

specific other diseases and exposures to VOCs in drinking water. The proposed study has

limitations, primarily due to uncertainties related to exposure assessment and the potential

for response and non-response biases. However, steps will be taken to reduce these biases

when possible and to assess the impact of potential biases on the estimates of effect (i.e.,

RRs) and exposure-response relationships.

A differential nonresponse bias would occur if the response rate is related to both

disease status and exposure status. For example, if those exposed with health problems have a higher response rate than either those exposed without health problems or those unexposed with health problems, then a bias away from the null would result. To minimize the possibility of differential nonresponse, ATSDR will request that the highest ranking officer of the USMC sign the introductory letter to encourage participation among former active duty Marines, including those without health problems. However, although important to the success of this study, achieving a high participation rate will not necessarily eliminate non-response (or selection) biases. Therefore, sensitivity analyses will be conducted to assess the possible impact of non-response biases.

Confirming disease reports will be crucial to the success of this study. ATSDR will work with the DOD and VA cancer registries as well as the cancer registries in all 50 states and the District of Columbia to set up a mechanism for confirming self-reported cancers. For non-cancer outcomes, the survey will obtain information that should facilitate the confirmation of these outcomes. ATSDR will also seek the assistance of the VA and the Naval Health Research Center to confirm these outcomes.

Ascertainment bias may be a problem if some participants do not accurately report diseases that they may have had (Bergmann et al. 1008; Desai et al. 2001; Freedman et al. 2006; Parikh-Patel et al. 2003; Schrijvers et al. 1994). In particular, there is a possibility that cancers and other conditions may be underreported. If underreporting is associated with exposure status, a differential bias would occur. To assess the impact of possible underreporting bias in the reporting of cancers, the rates of confirmed cancers in the exposed and unexposed groups will be compared to national rates. Anticipating that both response biases and underreporting of cancers may be problems, ATSDR is

considering conducting a cancer incidence data linkage study that would send the names and other identifying information of everyone in the study population (including those who do not respond to the survey) to the 50 state cancer registries and to the DOD and VA cancer registries. If the state and federal cancer registries agree to participate in this cancer incidence data linkage study, then ATSDR will develop a protocol and submit it for IRB approval.

Several sources of information will be used in the exposure assessment. The historical reconstruction of the Tarawa Terrace and Hadnot Point drinking water systems at Camp Lejeune, utilizing state-of-the-art contaminant fate, transport and distribution models, will provide the maximum likelihood monthly estimate of the level of each contaminant in each system as well as a 95% interval for each estimate based on Monte Carlo simulations. The exposure metrics used in this study will be based on these contaminant estimates. Information on the base residences and workplace locations will be obtained from the survey as well as from family housing records. Additional information on the locations where units were barracked and on workplace locations will be provided by current and former base staff and knowledgeable former Marines. No other information relevant to drinking water exposures at Camp Lejeune is available. The available information on exposures is sufficient to conduct a valid, scientifically sound study. However, exposure misclassification bias remains a possibility in this study. To reduce bias due to errors in the recall of residential/worksite address on base, the survey information will be supplemented by information from base family housing records and personnel records (e.g., unit identification codes and occupation codes). In addition, sensitivity analyses will be conducted to assess the impact of possible exposure

misclassification bias on the estimates of RR as well as exposure-response relationships.

While there is no direct public health benefit to those participants 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 populations. Only two populations have been studied with regard to the risk of adult cancers among those exposed to VOCs in drinking water. This study is unique because it will use monthly contaminant level estimates to define drinking water exposures.

USMC REGISTRANTS

The National Defense Authorization Act for Fiscal Year 2008 mandated that everyone who registered with the USMC receive a health survey. To comply with this law, ATSDR will mail health surveys to all registrants. However, registrants will not be included in the morbidity study unless they are also a member of the study population defined above. The surveys completed by registrants who are not members of the study population will be analyzed separately, primarily in a descriptive manner (i.e., demographics and the percent reporting each disease). Registrants will have separate informed consents (Appendix 6) and the Dillman Total Design Method will not be employed. Confirmation of reported diseases will not be sought for registrants who are not members of the study population.

DRAFT: DO NOT CITE OR QUOTE

REFERENCES

Agency for Toxic Substances and Disease Registry. (ATSDR) 1998. Volatile Organic Compounds in Drinking Water and Adverse Pregnancy Outcomes: U.S. Marine Corps Camp Lejeune. Onslow County, North Carolina. Atlanta: US Department of Health and Human Services.

Alexander DD, Mink PJ, Mandel JH, Kelsh MA. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. Occup Med Lond 2006;56:485-93.

Alexander DD, Kelsh MA, Mink PJ, Mandel JH, et al. A meta-analysis of occupational trichloroethylene exposure and liver cancer. Int Arch Occup Environ Health 2007; 81:127-43.

Asch DM, Jedrziewski MK, Christakis NA. Response Rates to Mail Surveys Published in Medical Journals. J Clin Epidemiol 1997; 50(10):1129-36.

Aschengrau A; Ozonoff D; Paulu C; et al. Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts [see comments]. Arch Environ Health 1993; 48:284-92.

Aschengrau A; Paulu C; Ozonoff D. Tetrachloroethylene-contaminated drinking water and the risk of breast cancer. Environ Health Perspect 1998; 106 Suppl 4:947-53.

Aschengrau A; Rogers S; Ozonoff D. Perchloroethylene-contaminated drinking water and the risk of breast cancer: additional results from Cape Cod, Massachusetts, USA. Environ Health Perspect 2003; 111:167-73.

Axelsson G. Use of questionnaires in a study of spontaneous abortion in a general population. J Epidemiol Community Health 1990; 44:202-204.

Bergmann MM, Calle EE, Mervis CA, Miracle-McMahill HL, Thun MJ, Heath CW. Validity of Self-reported Cancers in a Prospective Cohort Study in Comparison with Data from State Cancer Registries. Am J Epidemiol 1998; 147(6):558-62.

Blair A, Petralia SA, Stewart PA. Extended mortality follow up of a cohort of dry cleaners. Ann Epidemiol 2003; 13:50-6.

Boffetta P, Matisane L, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health 2003; 29:220-9.

Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. 1995. Public drinking water contamination and birth outcomes. Am J Epidemiol 141:850-62.

Cai P, König R, Boor PJ, Kondraganti S, et al. Chronic exposure to trichloroethene causes

early onset of SLE-like disease in female MRL +/+ mice. Toxicology and Applied Pharmacology 2008; 228:68–75.

California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Public Health Goal for Trichloroethylene in Drinking Water. February 1999.

California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Public Health Goal for Vinyl Chloride in Drinking Water. September 2000.

California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Public Health Goal for Benzene in Drinking Water. June 2001.

California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Public Health Goal for Tetrachloroethylene in Drinking Water. August 2001.

Checkoway H, Pearce N, Kriebel D. Research Methods in Occupational Epidemiology, 2nd ed. NY: Oxford U. Press, 2004.

Cohn P, Bove F, Klotz J, Berkowitz M, Fagliano J. 1993. Drinking water contamination and the incidence of leukemia and non-Hodgkin's lymphomas. NJDOH May 1993.

Cohn P, Klotz J, Bove F, Fagliano J. Drinking water contamination and the incidence of leukemia and non-Hodgkin's lymphoma. Environ Health Perspect 1994; 102:556-61.

Converse PD, Wolfe EW, Huang X, Oswald FL. Response Rates for Mixed-Mode Surveys Using Mail and E-mail/Web. American Journal of Evaluation 2008; 29(1):99-107.

Costas K, Knorr RS, Condon SK. 2002. A case-control study of childhood leukemia in Woburn, Massachusetts: the relationship between leukemia incidence and exposure to public drinking water. Sci Total Environ 300:23-35.

Defense Manpower Data Center (DMDC). DMDC Profile: Information and Technology for Better Decision Making. Department of Defense, Arlington VA and Seaside CA, 2004.

Desai MM, Bruce ML, Desai RA, Druss BG. Validity of Self-reported Cancer History: A Comparison of Health Interview Data and Cancer Registry Records. Am J Epidemiol 2001; 153(3): 299-306.

Dick FD. Solvent neurotoxicity. Occup Environ Med 2006;63:221-226.

Dillman DA. Mail and Internet surveys: The tailored design method (2nd ed., 2007 update). Hoboken, NJ: John Wiley & Sons, 2007.

Doebbeling B, Jones MF, Hall DB, Clarke WR, et al. Methodological issues in a population-based health survey of Gulf War veterans. J Clin Epidemiol 2002;55:477-487.

Doyle, P; Roman, E; Beral, V; et al. (1997) Spontaneous abortion in dry cleaning workers potentially exposed to perchloroethylene. Occup Environ Med 1997; 54:848-53.

Eaker S, Bergstrom R, Bergstrom A, Adami H, Nyren O. Response Rate to Mailed Epidemiologic Questionnaires: A Population-based Randomized Trial of Variations in Design and Mailing Routines. Am J Epidemiol 1998; 47(1):74-82.

Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S,Wentz R, Kwan I, Cooper R. Methods to increase response rates to postal questionnaires. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: MR000008. doi: 10.1002/14651858.MR000008.pub3.

Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, Kwan I. Increasing response rates to postal questionnaires: systematic review. BMJ 2002; 324:1183.

Evans BR, Peterson BL, Demark-Wahnefried W. No difference in response rate to a mailed survey among prostate cancer survivors using conditional versus unconditional incentives. Cancer Epidemiology Biomarkers & Prevention. 2004;13:277-278.

Fagliano J, Berry M, Bove F, Burke T. Drinking water contamination and the incidence of leukemia: an ecologic study. Am J Public Health 1990; 80:1209-1212.

Filip JC, Ming ME, Levy RM, Hoffstad OJ, Margolis DJ. Mail Surveys Can Achieve High Response Rates in a Dermatology Patient Population. J INVESTIGATIVE DERMATOLOGY 2004; 122(1):39-43.

Fleming CM, Bowden M. Web-based surveys as an alternative to traditional mail methods. J Environ Manage 2007; doi: 10.1016/j.jenvman.2007.09.011.

Franco A, Costoya MA, Roca E. Estimating risk during showering exposure to VOCs of workers in a metal-degreasing facility. J Toxicol Environ Health Part A 2007; 70:627-37.

Freedman DM, Sigurdson AJ, Doody MM, Love-Schnur S, Linet MS. Comparison between cancers identified by state cancer registry, self-report, and death certificate in a prospective cohort study of US radiologic technologies. Int J Epidemiol 2006; 35(2):495-7.

Gait R, Maginnis C, Lewis S, et al. Occupational exposure to metals and solvents and the risk of motor neuron disease. A case-control study. Neuroepidemiology 2003;22:353–6.

Galea S, Tracy M. Participation rates in epidemiologic studies. Ann Epidemiol 2007;17:643-653.

Garabrant DH, Lacey JV, Laing TJ, Gillespie BW, et al. Scleroderma and solvent exposure among women. Am J Epidemiol 2003; 157:493-500.

Gash DM, Rutland K, Hudson NL, Sullivan PG, et al. Trichloroethylene: Parkinsonism and

Complex 1 Mitochondrial Neurotoxicity. Ann Neurol 2008; 63:184–92.

Glass DC, Gray CN, Jolley DJ, Gibbons C, Sim MR, Fritschi L, et al. Leukemia risk associated with low-level benzene exposure. Epidemiology 2003; 14(5):569-77.

Goh CL, Goon A. Trichloroethylene dermatotoxicology: an update. Expert Rev Dermatol 2008; 3:173-8.

Grosse Y, Baan R, Straif K, Secretan B, et al. Carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide. Oncology: The Lancet, August 2007; 8:679-80.

Groves RM. Nonresponse rates and nonresponse bias in household surveys. Public Opinion Quarterly 2006;70:646-675.

Harris RE, Hebert JR, Wynder EL. Cancer risk in male veterans utilizing the Veterans Administration medical system. Cancer 1989;64:1160-1168.

Hayslett MM, Wildemuth BM. Pixels or pencils? The relative effectiveness of Web-based versus paper surveys. Library & Information Science Research 2004; 26:73–93.

HEI Air Toxics Review Panel. 2007. Mobile-Source Air Toxics: A Critical Review of the Literature on Exposure and Health Effects. HEI Special Report 16. Health Effects Institute, Boston, Mass.

Hotopf M, Wessely S. Can epidemiology clear the fog of war? Lessons from the 1990-91 Gulf War. Int J Epidemiol 2005; 34:791-800.

Hourani L, Hilton S. Occupational and environmental exposure correlates of adverse live-birth outcomes among 1032 US Navy women. J Occup Environ Med 2000; 42:1156-1165.

Huebner WW, Wojcik NC, Rosamilia K, Jorgensen G, Milano CA. Mortality updates (1970–1997) of two refinery/petrochemical plant cohorts at Baton Rouge, Louisiana, and Baytown, Texas. J Occup Environ Med. 2004;46:1229–1245.

Infante PF. Benzene Exposure and Multiple Myeloma: A Detailed Meta-analysis of Benzene Cohort Studies. Ann. N.Y. Acad. Sci. 2006; 1076:90–109

Janulewicz PA, White RF, Winter MR, Weinberg JM. Risk of learning and behavioral disorders following prenatal and early postnatal exposure to tetrachloroethylene (PCE)-contaminated drinking water. Neurotoxicology and Teratology xx (2008) xxx–xxx (in press).

Kamijima M, Hisanaga N, Wang H, Nakajima T. Occupational trichloroethylene exposure as a cause of idiosyncratic generalized skin disorders and accompanying hepatitis similar to drug hypersensitivities. Int Arch Occup Environ Health 2007; 80:357–70.

Kan FW, Forkert PG, Wade MG. Trichloroethylene exposure elicits damage in epididymal epithelium and spermatozoa in mice. Histol Histopathol 2007;22:977-88.

Kang H, Magee C, Mahan C, Lee K, Murphy F, Jackson L, Matanoski G. Pregnancy outcomes among U.S. Gulf War veterans: A population-based survey of 30,000 veterans. Ann Epidemiol 2001; 11:504-11.

Kang HK, Li B, Mahan CM, Eisen SA, Engel CC. Health of US veterans of 1991 Gulf War: a follow-up survey in 10 years. J Occup Environ Med. 2009;51:401-410.

Kaplowitz MD, Hadlock TD, Levine R. A Comparison of Web and Mail Survey Response Rates. Public Opinion Quarterly 2004; 68(1):94-101.

Kettaneh A, Al Moufti O, Tiev KP, Chayet C, et al. Occupational exposure to solvents and gender-related risk of systemic sclerosis: A metaanalysis of case-controls studies. J Rheumatol 2007; 34:97-103.

Khan HA. Short Review: Benzene's toxicity: a consolidated short review of human and animal studies. Hum Exp Toxicol 2007; 26; 677-85.

Kochen, W., D. Kohlmuller, P. De Biasi, and R. Ramsay. The endogeneous formation of highly chlorinated tetrahydro-beta-carbolines as a possible causative mechanism in idiopathic Parkinson's disease. Adv. Exp. Med. Biol. 2003; 527:253-63.

Kongsved SM, Basnov M, Holm-Christensen K, Hjollund NH. Response Rate and Completeness of Questionnaires: A Randomized Study of Internet Versus Paper-and-Pencil Versions. J Med Internet Res 2007; 9(3):e25.

Landtblom AM. Exposure to organic solvents and multiple sclerosis. Neurology 1997;49(Suppl 2):S70-S74.

Larson PD, Chow G. Total cost/response rate trade-offs in mail survey research: impact of follow-up mailings and monetary incentives. Ind Mark Manage 2003; 32:533-7.

Lash, LH; Parker, JC. Hepatic and renal toxicities associated with perchloroethylene. Pharmacol Rev 2001; 53:177-208.

Li H, Dai Y, Huang H, Li L, et al. HLA-B*1301 as a Biomarker for Genetic Susceptibility to Hypersensitivity Dermatitis Induced by Trichloroethylene among Workers in China. Environ Health Perspect 2007; 115:1553–6.

Lynge E, Andersen A, Rylander L, Tinnerberg H, et al. Cancer in Persons Working in Dry Cleaning in the Nordic Countries. Environ Health Perspect 2006; 114:213–9.

Maldonado G, Greenland S. Simulation Study of Confounder-Selection Strategies

Am. J. Epidemiol.1993; 138: 923 - 936.

Mandel JH, Kelsh MA, Mink PJ, Alexander DD, et al. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a metaanalysis and review. Occup Environ Med 2006; 63:597–607.

Mehlman MA. Causal relationship between non-Hodgkin's lymphoma and exposure to benzene and benzene-containing solvents. Ann. N.Y. Acad. Sci. 2006; 1076:120–8.

Mundt KA, Birk T, Burch MT. Critical review of the epidemiological literature on occupational exposure to perchloroethylene and cancer. Int Arch Occup Environ Health 2003; 76:473-91.

Nakajima T, Yamanoshita O, Kamijima M, Kishi R, Ichihara G. Generalized skin reactions in relation to trichloroethylene exposure: a review from the viewpoint of drug-metabolizing enzymes. J Occup Health 2003; 45:8–14.

Nakash RA, Hutton JL, Jorstad-Stein EC, Gates S, Lamb SE. Maximising response to postal questionnaires – A systematic review of randomised trials in health research. BMC Medical Research Methodology 2006; doi:10.1186/1471-2288-6-5.

National Academy of Sciences/National Research Council. Assessing the human health risks of trichlroroethylene: key scientific issues. National Academies Press, Washington 2006.

Noonan CW, Sykes L, Hilsdon R. Motor neuron disease/amyotrophic lateral sclerosis: Preliminary review of environmental risk factors and mortality in Bexar County, Texas March 5, 2002. Health Investigations Branch, Division of Health Studies, Agency for Toxic Substances and Disease Registry. Available at: http://www.atsdr.cdc.gov/NEWS/alsreport.html#INTRODUCTION

Oshiro WM, Krantz QT, Bushnell PJ. Characterization of the effects of inhaled perchloroethylene on sustained attention in rats performing a visual signal detection task. Neurotoxicology and Teratology xx (2008) xxx–xxx (in press).

Parikh-Patel A, Allen M, Wright WE, California Teachers Study Steering Committee. Validation of Self-reported Cancers in the California Teachers Study. Am J Epidemiol 2003; 157(6): 539-45.

Park RM, Schulte PA, Bowman JD, Walker JT, Bondy SC, Yost MG, Touchstone JA, and Dosemeci M. Potential occupational risks for neurodegenerative diseases. Am. J. Ind. Med. 2005;48:63–77

Paulu, C; Aschengrau, A; Ozonoff, D. Tetrachloroethylene-contaminated drinking water in Massachusetts and the risk of colon-rectum, lung, and other cancers. Environ Health Perspect 1999;107:265-71.

Perrin, MC; Opler, MG; Harlap, S, et al. Tetrachloroethylene exposure and risk of schizophrenia: Offspring of dry cleaners in a populaton birth cohort, preliminary findings. Schizophr Res. 2007; 90:251-4.

Reif JS, Burch JB, Nuckols JR, Metzger L, et al. Neurobehavioral effects of exposure to trichloroethylene through a municipal water supply. Environmental Research 2003; 93:248–58.

Reutman SR, LeMasters GK, Knecht EA, Shukla R, Lockey JE, Burroughs GE, Kesner JS. Evidence of Reproductive Endocrine Effects in Women with Occupational Fuel and Solvent Exposures. Environ Health Perspect 2002;110:805–811.

Rinsky RA, Hornung RW, Silver SR, Tseng CY. Benzene exposure and hematopoietic mortality: A long-term epidemiologic risk assessment. Am J Ind Med 2002; 42(6):474-80.

Rothman KJ, Greenland S (eds). Modern Epidemiology, 2nd ed. Philadelphia: Lippincott-Raven, 1998.

Rosoff PM, Werner C, Cliff EC, Guill AB, Bonner M, Demark-Wahnefried W. Response Rates to a Mailed Survey Targeting Childhood Cancer Survivors: A Comparison of Conditional versus Unconditional Incentives. Cancer Epidemiol Biomarkers Prev 2005;14(5):1330-2.

Ruder, AM; Ward, EM; Brown, DP. Mortality in dry-cleaning workers: an update. Am J Ind Med 2001; 39:121-32.

Ruder AM. Potential Health Effects of Occupational Chlorinated Solvent Exposure. Ann. N.Y. Acad. Sci. 2006; 1076:207–27.

Ryan MAK, Smith TC, Smith B, Amoroso P, Boyko EJ, Gray GC, Gackstetter GD, Riddler JR, Wells TS, Gumbs G, Corbeil TE, Hooper TI. Millennium Cohort: enrollment begins a 21-year contribution to understanding the impact of military service. J Clin Epidemiol 2007; 60:181-91.

Sallmén M, Lindbohm ML, Kyyronen EN et al. Reduced fertility in women exposed to organic solvents. Am J Ind Med 1995;27:699–713

Sallmén M, Neto M, Mayan ON. Reduced fertility among shoe manufacturing workers. Occup Environ Med 2008;65:518-524.

Scelo G, Constantinescu V, Csiki I, Zaridze D, et al. Occupational exposure to vinyl chloride, acrylonitrile and styrene and lung cancer risk (Europe). Cancer Causes Control 2004; 15:445-52.

Schonlau M, Asch BJ, Du C. Web Surveys as Part of a Mixed-Mode Strategy for

Populations That Cannot Be Contacted by E-Mail. Social Science Computer Review 2003; 21(2): 218-22.

Schrijvers CTM, Stronks K, van de Mheen DH, Coebergh JWW, Mackenbach JP. Validation of Cancer Prevalence Data from a Postal Survey by Comparison with Cancer Registry Records. Am J Epidemiol 1994; 139(4): 408-13.

Shih TH and Fan X. Response Rates and Mode Preferences in Web-Mail Mixed-Mode Surveys: A Meta-Analysis. Int J Internet Sci 2007; 2(1):59-82.

Shih TH and Fan X. Comparing response rates from web and mail surveys: a meta-analysis. Field Methods 2008;20:249-271.

Smith B, Smith TC, Gray GC, Ryan MAK. When Epidemiology Meets the Internet: Web-based Surveys in the Millennium Cohort Study. Am J Epidemiol 2007; 166(11):1345-54.

Smith EM, Hammonds-Ehlers M, Clark MK, Kirchner HL, Fuortes L. Occupational exposures and risk of female infertility. J Occup Environ Med. 1997 Feb;39:105-7.

Sonnenfeld N, Hertz-Picciotto I, Kaye W.E. Tetrachloroethylene in Drinking water and Birth outcomes at the US Marine Corps Base at Camp Lejeune North Carolina. Am J Epidemiol 2001; 154(10):902-8.

Steffen AD, Kolonel LN, Nomura AM, Nagamine FS,Monroe KR, Wilkens LR. The Effect of Multiple Mailings on Recruitment: The Multiethnic Cohort. Cancer Epidemiol Biomarkers Prev 2008;17(2):447–54.

Steinmaus C, Smith AH, Jones RM, Smith MT. Meta-analysis of benzene exposure and non-Hodgkin's lymphoma: Biases could mask an important association. Occup. Environ. Med. 2008 (in press).

Tao X, Massa J, Ashwell L, Davis K, Schwab M, Geyh A. The World Trade Center clean up and recovery worker cohort study: Respiratory health amongst cleanup workers approximately 20 months after initial exposure at the disaster site. J Occup Environ Med 2007;49:1063-1072.

Wang G, Ansari GAS, Khan MF. Involvement of lipid peroxidation-derived aldehyde-protein adducts in autoimmunity mediated by trichloroethene. Journal Toxicol Environ Health, Part A, 2007; 70:1977–85.

Wartenberg D, Reyner D, Scott CS. Trichloroethylene and Cancer: Epidemiologic Evidence. Environ Health Perspect 2000; 108(suppl 2):161-76.

Weisel CP, Jo W-K. Ingestion, inhalation, and dermal exposures to chloroform and trichloroethene from tap water. Environ Health Perspect 1996; 104:48–51.

World Health Organization (WHO). Tetrachloroethene: Concise International Chemical Assessment Document 68. Geneva 2006.

World Health Organization (WHO). Trichloroethene in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality. 2005.

Table 1. Minimum Detectable Incidence Rate Ratio ("RR")

% disease in the unexposed	Cancers[*]	10% unexposed[**]	20% unexposed[**]	25% unexposed[**]	30% unexposed[**]
.08%	Brain, Leukemias	1.62	1.57	1.56	1.55
.22%	Colon & Rectum	1.35	1.33	1.32	1.32
.02%	Esophagus, Larynx, Multiple Myeloma	2.43	2.32	2.29	2.26
.09%	Kidney, Oral	1.58	1.53	1.52	1.51
.03%	Liver	2.11	2.02	2.00	1.98
.20	Lung, Thyroid	1.37	1.34	1.34	1.33
.24%	Melanoma	1.33	1.31	1.30	1.30
.16%	Non-Hodgkin's lymphomas	1.42	1.39	1.38	1.37
.04%	Pancreas, Stomach	1.93	1.86	1.84	1.82
.06%	Urinary Bladder	1.73	1.67	1.66	1.65

[*] More than one cancer type may have the same estimated incidence in the unexposed.
[**] % unexposed among those who resided, worked or were stationed at Camp Lejeune. This group is then added to those who were stationed at Camp Pendleton. For example, assuming 247,000 from Camp Lejeune and 60,000 from Camp Pendleton, and assuming a 65% participation rate, then approximately 160,550 from Camp Lejeune and 39,000 from Camp Pendleton will respond to the survey. The "10% unexposed" includes the 39,000 from Camp Pendleton and 10% of the Camp Lejeune participants (i.e., 16,055), for a total of 55,055 unexposed.

The **minimum detectable risk ratio** was calculated based on a type 1 error of .10 (equivalent to a 90% confidence interval or a p-value, two-tailed of .10) and a type 2 error of .10 (equivalent to 90% statistical power).

The incidences in the unexposed group were estimated based on the age-specific, 1999-2004 U.S. cancer incidence rates (all genders and race/ethnicity groups combined) from the National Program of Cancer Registries, CDC and the following assumptions:

1. The health survey instrument would be mailed to approximately 307,000 including 60,000 from Camp Pendleton;
2. Participation rate would be 65%
3. The average participant first resided or worked at the base at age 19 in 1980. (This assumption is based on the fact that the majority of those receiving the survey were active duty Marines and Navy personnel who were stationed at the base anytime between 1975 and 1985 and who started active duty in 1975 or later.)
4. Follow-up begins 10 years after first resided or stationed at the base (i.e., a 10-year latency period)
5. The follow-up period for the average participant therefore begins in 1990 (age 29) and continues until 2008 (age 47).
6. Cancer rates for the unexposed are similar to national rates.