An Assessment of the Feasibility of Conducting Future Epidemiological Studies at USMC Base Camp Lejeune

By

Frank J. Bove, Sc. D

Perri Zeitz Ruckart, MPH

Division of Health Studies

Agency for Toxic Substances and Disease Registry (ATSDR)

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Executive 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. In 2005, a panel of independent scientists convened by ATSDR recommended that the agency

- identify cohorts of individuals 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 at the base.

In response, ATSDR has prepared this assessment of the feasibility of conducting future epidemiological studies at the base. ATSDR visited the Naval Health Research Center (NHRC), the Defense Manpower Data Center (DMDC), and the DOD Education Activity storage facility at Fort Benning, Georgia, to determine whether available databases could identify adults and children who lived at the base, or civilians who worked at the base, during the period when drinking water was contaminated with VOCs. ATSDR also convened a panel of epidemiologists with experience in military and occupational cohort studies to provide recommendations on future studies. The list of participants and the panel's minutes are provided in Appendix A.

ATSDR concludes that a mortality study and a cancer incidence study are feasible. Available DOD personnel databases can identify active duty Marines and naval personnel and civilian employees stationed at the base during the period when the Hadnot Point and Tarawa Terrace drinking water systems were contaminated with VOCs. ATSDR also concludes that it may be feasible to include in the cancer incidence study those who participated in the ATSDR 1999–2002 survey and those who will participate in the congressionally mandated Navy/Marine Corps health survey scheduled for 2009. These studies should have sufficient statistical power to detect moderate excesses (e.g., standardized mortality ratios [SMRs] < 2.0) in specific cancers among those exposed to the contaminated drinking water (see Appendix B).

A literature review conducted for this assessment has identified specific cancers (e.g., leukemia, non-Hodgkin's lymphoma, bladder cancer, breast cancer, and lung cancer) that have been associated with occupational or drinking water exposures to trichloroethylene (TCE) or tetrachloroethylene (perchloroethylene or PCE). These cancers could be evaluated in a mortality study and in a cancer incidence study. The literature review also identified noncancer diseases associated with TCE or PCE occupational exposures (e.g., scleroderma, kidney and liver diseases) that could be studied using the Navy/Marine Corps health survey.

Several criteria were used to determine the feasibility of conducting future epidemiological studies at the base. The criteria reflect ATSDR's commitment to conduct excellent and scientifically credible science. These *feasibility criteria* include

- Minimize bias in the selection of persons into the cohort(s).

- Minimize bias in the health information obtained for each cohort member.
- Minimize bias due to risk factors other than drinking water exposures.
- Minimize bias in the assessment of exposures.
- Ensure sufficient statistical power to detect small excesses in disease rates.

In general, future epidemiological studies at the base should be capable of

1. Producing scientific knowledge capable of generalization to similar situations elsewhere involving the particular exposures and diseases, and
2. Answering the affected community's specific questions concerning a possible link between the drinking water exposures and diseases in that community.

All-Causes Mortality Study

The proposed mortality study would evaluate all causes of death occurring in the cohort of Marines and naval personnel who began active duty on or after June 1975 and who were assigned to the base anytime during the period June 1975– December 1985. The study would also evaluate a cohort of civilians whose employment start-date was on or after June 1974 and who worked at the base anytime during the period June 1974–December 1985. These cohort definitions are based on the availability of computerized personnel records at the DMDC and on the period of drinking water contamination at the base.

Because their drinking water exposure experiences were different, these two cohorts would be analyzed separately. The focus of the analyses would be comparisons between those exposed and those unexposed within each cohort (i.e., "internal comparisons"). Internal comparisons avoid biases due to the "healthy veteran effect" caused by differences in underlying mortality rates between veterans and the general public. **Nevertheless, to improve the credibility of the mortality study, the epidemiology panel recommended including in the mortality study and in the cancer incidence study an external, unexposed comparison group, similar in all respects to the Marines and to the civilian workers at Camp Lejeune—except for exposure to VOC-contaminated drinking water.** ATSDR therefore proposes sampling approximately 50,000 Marines and 10,000 civilians from those who were first stationed or employed at Camp Pendleton, California, during the period 1975–1985 and who, during the period of drinking water contamination, were never stationed at Camp Lejeune.

The inclusion of the Camp Pendleton samples would address two major issues: 1) whether statistical power for the internal comparisons is inadequate because too few members of the Camp Lejeune cohorts were unexposed to the drinking water contamination, and 2) whether anyone was *un*exposed to contaminated drinking water at the base (e.g., because of water consumption during field training or because Hadnot Point water resupplied the Holcomb Boulevard system during summer months when the golf courses were irrigated).

To determine vital status, personal identifiers for each cohort member (i.e., name, social security number (SSN), date of birth, and sex) would be matched using a customized algorithm to data in the Veterans Affairs (VA) Beneficiary Identification and Record Locator Subsystem (BIRLS) death file, the Medicare Vital Status file, and the Social Security Administration (SSA) Death Master File. Follow up would begin at the start of known assignment at Camp Lejeune and continue to the end of the study period, to December 31, 2007, to the date of death, or to the date of last known vital status. Exposures may be lagged in the analyses to account for a latency period. The National Death Index (NDI) would be used to determine the cause of death. Death certificates would also be obtained. For deaths occurring before the start of the NDI in 1979, a nosologist would code the cause of death from the death certificate. Appendix J describes the VA, Medicare, SSA, and NDI databases. The minimum detectable SMRs for comparisons between the Camp Lejeune active duty cohort and the U.S. population are presented in Appendix B.

For the active duty cohort, the exposure assessment would be based on the monthly levels of contaminants in the drinking water serving their residence (e.g., family housing or barracks). For the civilian cohort, the exposure assessment would be based on the monthly contaminant levels in the drinking water serving the workplace location.

Cancer Incidence Study

A cancer incidence study would evaluate all confirmed cancers newly diagnosed during the period from the date of first residence or employment at Camp Lejeune (or Camp Pendleton) to December 31, 2007 (i.e., the most recent date when complete data are available from state and federal cancer registries) or date of death. This study would use two approaches: 1) data linkage with state cancer registries and federal cancer registries; and 2) conduct of the congressionally mandated Navy/USMC health survey. For the data linkage approach to be successful, either the participation of all 50 state cancer registries or the registries in the states where a sizeable percentage of Marine retirees reside would be necessary (e.g., the first 25–30 states listed in Appendix C). If the data linkage approach is not successful, the cancer incidence study would be based solely on the health survey. On the other hand, if the health survey is unsuccessful, the cancer incidence study would be based solely on the data linkage approach. For the health survey to be successful, a participation rate of at least 65% is necessary. To increase survey participation, methods such as repeat mailings and phone contacts would be employed. If both approaches are successful, then they could be combined.

1. *Data Linkage*

This approach would match each cohort member's personal identifier information to the available data on cancers from all 50 state cancer registries, federal (DOD and VA) cancer registries, death certificates, and the NDI. Appendix J describes these cancer information sources. If participation of all 50 state cancer registries cannot be achieved, then it would be necessary to gain the participation of the 25–30 states with the highest percentage of Marine Corps retirees (see Appendix C).

The cohorts evaluated in the mortality study would be included in this study (together with the samples from Camp Pendleton). The minimum standardized incidence ratios (SIRs) for comparisons between the Camp Lejeune active duty cohort and the U.S.

population are presented in Appendix B. Because the number of women in the active duty cohort is small (i.e., approximately 8,000), statistical power to detect female cancers would not high. Therefore, ATSDR would add to the active duty cohort about 2,900 women who responded to the ATSDR 1999–2002 survey of parents of children who were carried or conceived at Camp Lejeune during 1968–1985 *and* who 1) first resided at the base between 1975 and 1985, and 2) provided ATSDR with their SSNs.

All state cancer registries have data available from 1997 onward. Therefore, comparisons (SIRs and standardized incidence odds ratios) could be made between national cancer rates and cancer rates among the Lejeune and Pendleton cohorts for the period 1997–2007. Comparisons internal to the Lejeune cohorts (i.e., between the exposed and unexposed)—and comparisons between Camp Lejeune and Camp Pendleton—would utilize all cancers identified during the entire study period, 1975–2007.

Because most of the cancer registries do not cover the entire study period, some cancers would be missed. Still, because the cohort members were very young at the start of follow up, the number of missed cancers would be low. In addition, for the internal comparisons bias due to missed cases would be minimal; there should be no relation between exposure status and the states where cohort members reside after retiring from service. On the other hand, the comparison between Camp Lejeune and Camp Pendleton could be affected by such a bias if differences appear between the two bases in the percentage of retired Marines migrating to states with older cancer registries. Although residences after retirement are not available from the DOD databases, it is possible to compare the home state frequencies of Marines stationed at the two bases to determine any significant geographical differences.

2. *Combined Data-Linkage and Health Survey Approach*

If the Navy/USMC health survey achieves at least a 65% participation rate, then the cancer incidence study will include those who complete the survey as well as all who are included in the data linkage approach. The personal identifier information for the health survey participant will be matched to the available data on cancers from the state cancer registries and the federal (DOD and VA) cancer registries. Cancers identified in the mortality study will be included, and the next of kin listed on the death certificate will be sent a health survey to collect risk factor information on the deceased case.

The health survey will be mailed to the active duty and civilian cohorts, to the Camp Pendleton sample, to the 12,598 respondents in the 1999–2002 ATSDR survey, and to anyone who registered with the USMC or who provided contact information to ATSDR. The health survey will collect information on any cancer a person may have had that was diagnosed by a health provider. Such information will include the type of cancer, the date of diagnosis, and the state and hospital of diagnosis (to facilitate the acquisition of cancer registry data or medical record confirmation). Self-reported cancers will be confirmed by medical records or cancer registrations. 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. Other items in the survey will include a residential history, residences at the base, an occupational history, and information on several risk factors (e.g., SES, demographics, smoking, alcohol consumption).

In effect, this will be a "two-stage" approach in which information on exposures and cancers will be available for everyone in the study who is not lost to follow up. Information on potential confounders such as occupational exposures and smoking, however, will only be available to those who complete the health survey. Yet information on potential confounders from those who complete the health survey can still be used to adjust for confounding in the analyses of the entire study population.

To determine the most cost-effective method by which to enhance participation, the survey will be mailed to a small sample of the Camp Lejeune and Camp Pendleton cohorts. Various methods for converting nonrespondents will be tested to determine cost-effectiveness: repeat mailings, phone contacts, incentives, and an introductory letter signed by the Commandant of the Marine Corps encouraging participation. The effectiveness of using a mixed mode approach (e.g., a mailed survey and a Web-based survey) will also be evaluated.

Other Diseases

In addition to questions on cancers, the health survey will include questions on those nonfatal diseases that can be confirmed by medical records and that are known or suspected of being associated with solvent exposures. These diseases will include Parkinson's disease, kidney failure and other severe kidney diseases, severe liver diseases, lupus, and scleroderma. The survey form will also allow the respondent to report other disease conditions. The survey may also include a few symptom questions such as skin disorders and neurological disorders with a known relation to solvent exposure.

Introduction

This report describes the activities and the conclusions of ATSDR's feasibility assessment of future drinking water epidemiological studies at the U.S. Marine Corps Base Camp Lejeune, North Carolina. The feasibility assessment's goal was to determine whether data exist to conduct scientifically credible epidemiological studies. Those studies would assess the biologically plausible adverse health effects of exposures to the drinking water contaminants in the Camp Lejeune water systems. The feasibility assessment assumed that the historical reconstruction of drinking water contamination in the Tarawa Terrace and Hadnot Point systems would provide sufficient data to determine exposures. Therefore, the feasibility assessment focused on two key questions:

1. Are the data sufficient to identify members of each of the cohorts (adults, children) who resided or who worked at the base, and who while there were potentially exposed to contaminated drinking water?
2. Are the data sufficient to ascertain and to confirm biologically plausible adverse health outcomes[1] related to exposures to the volatile organic compounds (VOCs) detected in the Camp Lejeune water systems?

Site History

The United States Marine Corps (USMC) Base at Camp Lejeune, North Carolina began operations during the early 1940s. Currently, the base is home to an active duty, dependent, retiree, and civilian employee population of nearly 150,000 persons: about 43,000 are active military personnel and, together with their dependents, total about 53,500. About 42,000 base residents are retired, and about 4,900 are civilian employees. The base has a relatively young population—almost two-thirds of the active military personnel and their dependents are under the age of 25. Considerable in- and out-migration occurs at the base. For example, ATSDR was told by staff of the Camp Lejeune Naval Hospital that during the 1970s and 1980s, an estimated one-third of mothers receiving prenatal care at the hospital were transferred from Camp Lejeune before delivery. The average duration in family housing is about 2 years. On leaving the base, people scatter across the nation, becoming potentially exposed to pollution in military and nonmilitary jobs as well as to pollution occurring in other parts of the country.

Before March 1987, eight water treatment plants provided drinking water to family housing units and barracks at the base: Tarawa Terrace (TT), Hadnot Point (HP), Holcomb Boulevard (HB), Courthouse Bay, Rifle Range, Onslow Beach, Montford Point/Camp Johnson and New River (see Appendix H). During the base's 1980–1985 sampling program, volatile organic compounds (VOCs) were detected in HP and TT wells and in their water distribution systems. The primary contaminant in the TT system was tetrachloroethylene (also known as perchloroethylene or PCE). The primary contaminant in the HP system was trichloroethylene (TCE). Other major contaminants in the HP system included trans-1,2-dichloroethylene (DCE), PCE, and benzene. By early February 1985 the most contaminated wells in the HP and TT systems were shut down.

An important feature of the contamination of these two drinking water systems was its intermittent nature. To supply water on any given day, each system had many more wells than

[1] (i.e., known or suspected outcomes based on experimental or observational studies or both)

were necessary. Wells were rotated in and out of service. Contamination levels in the drinking water distribution system varied depending on the wells being used at a particular time. In each system, before treatment and distribution water from all the wells in use was mixed.

The HP system was constructed in the 1940s, the TT system was constructed in 1952, and the HB system was constructed in June 1972. Before June 1972, the HB service area was supplied by the HP system. The wells serving the HB system were not contaminated. During dry summer months, however, the HB system's supply was depleted due to irrigation of the base's golf courses. On these occasions, contaminated water from HP resupplied the HB system. How often this interconnection between the HP and HB system was used to resupply the HB system during dry summer months is currently not known. On January 27, 1985, a fuel pump broke at the HB system and VOC-contaminated water from HP was supplied to the HB service area for about 2 weeks while repairs were made.

No organic solvent contamination was detected in the drinking water from the other treatment plants serving the base.

Hadnot Point (HP)

The Hadnot Point system served most of the on-base bachelor officer's quarters, the enlisted barracks, and the family housing units at Hospital Point. Before June 1972, Hadnot Point also served family housing areas subsequently served by the Holcomb Boulevard system. At present, when the contamination of the Hadnot Point system wells began is unknown, but the contamination could have started as early as the late 1940s or early 1950s. During the 1940s and 1950s, underground storage tanks were installed at Hadnot Point and used to store waste degreasing solvents. The possible sources of contamination of the Hadnot Point system were leaking underground storage tanks, spills, and other waste disposal practices. By mid-2009 modeling of this system will be complete. The model will determine when contamination started and will estimate monthly contaminant levels.

In October 1980, the base began sampling the Hadnot Point system for trihalomethanes (THMs), a chlorination disinfectant byproduct. The analysis of the sample at Hadnot Point indicated the presence of VOCs other than THMs. Samples taken in 1981 also indicated the presence of VOCs other than THMs in the Hadnot Point system. In April 1982, the base began using a different laboratory for the analyses of drinking water samples. TCE was detected at 1,400 ppb and PCE was detected at 15 ppb—slightly above its detection limit of 10 ppb. No action was taken at the time; in 1982 water quality standards had not been established for these VOCs.

In July 1982, TCE was detected at levels around 20 ppb, much lower than the level detected in the sample taken just a few months earlier. THM samples taken at Hadnot Point in November 1982 and in 1983 were found to be contaminated with TCE and PCE. In November 1984, the base received results of samples taken in July 1984. In one well at Hadnot Point, both TCE and benzene were detected. Among the contaminated wells at Hadnot Point and finished water at one building served by the Hadnot Point system, TCE levels ranged from 5 ppb to 1,600 ppb.

In December 1984, some of the Hadnot Point wells were shut down or placed offline. On January 27, 1985, a fuel pump broke at the Holcomb Boulevard system, and while repairs were made, water from Hadnot Point was supplied to the Holcomb Boulevard service area. On January 31, 1985, buildings in the Holcomb Boulevard service area that were temporarily receiving water from Hadnot Point were sampled. High contamination was found at the Berkeley Manor Elementary School (1,148 ppb TCE and 407 ppb 1,1-dichloroethene [DCE]), an Officer's club (890 ppb TCE and 332 ppb DCE), the Married Officers Quarters (1,041 TCE), and two Berkeley Manor Housing Units (905 ppb and 981 ppb TCE, 335 ppb and 369 ppb DCE). In early February 1985, all contaminated wells in the Hadnot Point system were closed.

Tarawa Terrace (TT)

The Tarawa Terrace water system served the family housing units in Tarawa Terrace and in the Camp Knox trailer park. In the early 1950s, a supply well for the Tarawa Terrace family housing units was installed about 900 feet from a septic tank belonging to ABC One-Hour Cleaners (ABC), a local dry cleaning firm. ABC began operation near the base in 1953. Contamination of the supply well near ABC likely began soon after the well's installation. During May, 1982 distribution system sampling, PCE was detected at 80 ppb. In July 1982, distribution system samples found levels of PCE in the range of 76 ppb to 104 ppb. Distribution system samples taken on February 5, 1985 detected 215 ppb PCE, 8 ppb TCE, and 12 ppb trans-1,2-dichloroethylene (t-DCE). On February 8, 1985, the two most contaminated wells were taken offline, and later in 1985 ABC discontinued use of the septic tank. The Tarawa Terrace system was closed in March 1987.

In July 2007, ATSDR released "Chapter A: Summary of Findings" of the historical reconstruction of the Tarawa Terrace system (ATSDR 2007). After extensive modeling of the fate and transport of the groundwater contaminants and the production of the drinking water wells, ATSDR concluded that by November 1957 PCE in the Tarawa Terrace water distribution system had reached the 1992 U.S. Environmental Protection Agency (EPA) maximum contaminant level (MCL) of 5 ppb. (http://www.atsdr.cdc.gov/sites/lejeune/docs/WTP%20Concetrations_Table.pdf). Except for July–August 1980 and January–February 1983, the MCL was exceeded in the distribution system every month from November 1957 until mid-February 1985. Because of limited field data, the model results are uncertain. Probabilistic and sensitivity analyses indicated, however, that the uncertainty was within acceptable limits, and the model results were, therefore, highly reliable (ATSDR 2007).

In March 1984, the maximum PCE level in the distribution system was estimated from the model as a monthly average of 183 ppb. Estimates of the maximum monthly average levels of degradation products of PCE in the distribution system were as follows: 7 ppb TCE, 22 ppb tDCE, and 12 ppb vinyl chloride. The model estimated that monthly average levels of PCE exceeded 5 ppb for most of the months between March 1985 and February 1987, but during this period USMC sampling found levels below the 10 ppb-detection limit.

1998 ATSDR Study of Adverse Birth Outcomes ("SGA Study")

ATSDR used North Carolina birth certificates and fetal death certificates for Onslow County during 1968–1985 and base family housing records to evaluate whether associations existed between potential maternal exposure to the drinking water contaminants at the base and

- preterm birth (<37 weeks gestational age),
- small for gestational age (SGA),

- mean birth weight deficit, and
- fetal death.

(ATSDR 1998; Sonnenfeld et al. 2001).

Using published sex-specific growth curves for whites in the state of California, SGA was determined as <10th percentile weight by gestational week. The study was completed and published as an ATSDR report in August 1998.

The fetal deaths evaluation was abandoned because 1) the total number of fetal deaths identified through the computerized state database was small (N=83), 2) the cause of death was missing for most of the fetal deaths, and 3) a review of race-specific U.S. rates during the study period showed that the number of observed fetal deaths in the computerized database was considerably lower (between 40% and 50% fewer) than expected.

During the period January 1, 1968 through December 31, 1985, the study obtained electronic birth certificate information for 12,493 live births born to women who resided in base family housing at time of delivery. After exclusions for poor data quality, the analyses included 11,970 live births. The year 1968 was chosen as the starting point of the study because 1) that was the year that North Carolina began computerizing some of the data items in its birth records, 2) although ATSDR did not know when contamination began in the drinking water systems, ATSDR was certain that it existed by 1968, and (3) the number of births during 1968–1985 was large enough to achieve sufficient statistical power for the analyses of SGA and preterm birth. Information from the birth certificate was used to determine birth weight and gestational age. Birth certificates were linked to the base's family housing records by mother's address at delivery and, in most cases, father's name. The housing records contained dates of occupancy and military pay grade for the family member assigned to the unit (i.e., the active duty person). This information was used to estimate the dates during pregnancy when the mother resided in the base housing unit.

The study estimated that mothers of 6,117 births resided at Tarawa Terrace for at least 1 week before birth occurred. These births were considered exposed to PCE. Mothers of 31 births who resided at the Hospital Point family housing area (served by the Hadnot Point system) for at least one week before birth occurred were considered having "long-term" exposure to TCE. Mothers of 141 births who resided in housing units supplied briefly in 1985 by the Hadnot Point system when the Holcomb Boulevard system was down (due to a fuel pump failure) for at least one week before birth occurred were considered having "short-term" exposure to TCE. Mothers of 5,681 births (nearly half of the total number of births on base during the study period) resided in family housing units in the Holcomb Boulevard system service area from 1968 through December 1984 and were considered unexposed to VOCs in drinking water.

The study found that "long-term" TCE exposure from Hadnot Point water was associated with an elevated risk for SGA (OR=3.9, 90% CI: 1.1, 11.9) only among male infants (ATSDR 1998). Exposure to PCE from Tarawa Terrace 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 previous fetal losses (adjusted OR=2.5, 90% CI: 1.5, 4.3) (Sonnenfeld et al. 2001). The following potential confounders and effect modifiers were included: sex of infant, maternal and paternal ages, maternal race, maternal and paternal education, military pay grade, maternal parity, adequacy of prenatal care, marital status, and year of birth.

Mothers of 5,681 births (nearly half of the total number of births on base during the study period) resided in family housing units in the Holcomb Boulevard system service area from 1968 through December 1984 and were considered unexposed to VOCs in drinking water. At the time the study was conducted, ATSDR did not know when the Holcomb Boulevard system went online—it was assumed to be online by 1968. Information later obtained during the historical exposure reconstruction of the Tarawa Terrace system indicated that the Holcomb plant came online in June 1972. Before that date, this housing area was served with contaminated water from Hadnot Point. In addition, contaminated water from the Hadnot Point system may have resupplied the Holcomb Boulevard system during dry summer months when water from Holcomb Boulevard was used to irrigate base golf courses. How frequently the interconnection between these two systems was used for this purpose is currently unknown.

Because many of the births occurring to families living in the Holcomb Boulevard service area were mistakenly considered unexposed, the SGA study will be reanalyzed using the information and the monthly contaminant estimates from the Tarawa Terrace and Hadnot Point historical exposure reconstructions. It is possible that the PCE findings may not change greatly after this reanalysis. The original study did a separate analysis of PCE and SGA for 1982–1985, and the results were similar to the results obtained for the entire study period. On the other hand, because the number of births exposed to TCE will increase from 31 in the original study to over 1,000 for the reanalysis, it is expected that substantially different results for TCE should be observed.

In addition, the original study did not have monthly estimates of contamination levels but simply compared exposed to unexposed. Thus when monthly contamination levels are evaluated the reanalysis may result in different findings for PCE and TCE.

Current ATSDR Epidemiological Study of Specific Birth Defects and Childhood Leukemia/NHL

To evaluate birth defects and childhood cancers, ATSDR initiated a multi-step process. First, a review of the scientific literature was conducted to narrow the focus of potential adverse outcomes to study. Second, a telephone survey was conducted to identify potential cases of the selected adverse childhood outcomes among the births occurring during 1968–1985 to mothers residing at the base anytime during their pregnancy.

The next step was to use medical records to verify the diagnoses of the self-reported cases ascertained by the survey. At the same time, the historical exposure reconstruction of the Tarawa Terrace and Hadnot Point systems was being conducted.

The review of the toxicological and epidemiological literature (ATSDR 2005c)—in particular the few epidemiological studies of adverse reproductive outcomes and exposures to VOC-contaminated drinking water— supported the evaluation of the following health outcomes in children:

- neural tube defects or "NTD" (i.e., spina bifida excluding spina bifida occulta; anencephaly; and encephalocele),
- oral cleft defects (i.e., cleft palate and cleft lip with or without cleft palate),
- conotruncal heart defects (i.e., tetralogy of Fallot, D-transposition of the great arteries, truncus arteriosus, pulmonary valve atresia with ventricular septal defect, and double outlet right ventricle),

- choanal atresia,
- childhood leukemia, and
- childhood non-Hodgkin's lymphoma (NHL).

One NJ study found associations between TCE-contaminated drinking water, carbon tetrachloride-contaminated drinking water, and dichloroethylene-contaminated drinking water (1,1 and 1,2 DCE combined) and NTD and oral clefts (Bove et al. 1995; Bove et al. 2002). Major heart defects were associated with TCE-contaminated drinking water in Tucson, AZ and with benzene-contaminated water and 1,2-dichloroethane-contaminated water in the NJ study (Bove et al. 1995; Bove et al. 2002). A study of 1,1,1-trichloroethane-contaminated drinking water in Santa Clara County, CA, however, did not find associations with major heart defects (Swan et al. 1989). The Woburn study found an association between primarily TCE-contaminated drinking water and a cluster of choanal atresia, which is etiologically related to conotruncal heart defects (Bove et al. 2002). A NJ study also found a weak association between PCE-contaminated drinking water and oral clefts (Bove et al 1995).

Another NJ study and the Woburn study found an association between TCE-contaminated drinking water and childhood leukemia (Cohn et al. 1994; Costas et al. 2002). A study at Dover Township, NJ (NJDHSS 2003) also found an association between contaminated drinking water and childhood leukemia, but the drinking water contained an exotic chemical: styrene-acrylonitrile trimer (SAN trimer), as well as TCE and PCE. The toxicity of the SAN trimer, either alone or in mixture with TCE and PCE, is not known.

These few studies constitute the universe of epidemiological research on solvent-contaminated drinking water and birth defects and childhood cancers. This lack of research—and the obvious need for further research in these areas—affected the agency's ability to reconstruct historically the drinking water exposures at Camp Lejeune. Because of these conditions and the high levels of TCE and PCE drinking water contamination, ATSDR decided to conduct a study of specific birth defects and childhood cancers at the base.

A telephone survey ascertained cases of the specific birth defects of interest and childhood leukemia/NHL. The survey was necessary because 1) data from NC cancer and birth defect surveillance systems were not available until 1990 and 1996, respectively, and 2) a number of mothers who were pregnant while residing at Camp Lejeune were transferred off the base before delivery and gave birth outside NC. The telephone survey began in September 1999 and was completed in January 2002. The survey sought information on all children who were born during 1968–1985 to a mother who resided at the base anytime during her pregnancy. This included births at the base and births that occurred after the mother was transferred off the base.

ATSDR attempted to locate and contact the parents of each eligible child. ATSDR wanted to elicit information on the child's health as well as to confirm that the mother was a resident at the base at some point during the pregnancy. ATSDR also wanted to collect information on other potential confounders. Eligible children were identified in two ways. First, the survey used the birth certificate information from the previous Camp Lejeune study of SGA (ATSDR 1998). A total of 12,493 birth certificates were obtained for children born from 1968 through 1985 to mothers who lived in base housing at the time of delivery.

Second, children born from 1968 through 1985 to mothers whose pregnancies occurred while they lived in base housing but who lived off the base at the time of delivery were identified primarily by word-of-mouth (e.g., parent groups), by referrals from other parents during their interviews, or by parents prompted by media information about the survey (or by the USMC emails and notices) to contact ATSDR or the USMC. The number of these births occurring off the base is unknown. Camp Lejeune Naval Hospital staff estimated, however, that about one third of mothers receiving prenatal care at the hospital were transferred from Camp Lejeune before delivery. Using this information, ATSDR estimated that between 3,500 and 4,500 mothers were transferred from Camp Lejeune before delivery. Therefore, an estimated total of 16,000 to 17,000 births occurred among women who were pregnant while living at Camp Lejeune during the study period (ATSDR 2003).

ATSDR surveyed the parents of 12,598 eligible children. This represented an overall 74%–80% participation rate, depending on the estimate used for births that occurred off base. Of the 12,493 births that occurred on base, the survey was able to obtain information on 80.4%. Of the children born after the mother transferred off the base, information was obtained from 2,558. Assuming a total number of off-base births ranging from 3,500 to 4,500, this represented a participation rate of 64% to 73%. The survey demonstrated that an epidemiological study of this population could have high participation rates. Parents were asked if the child was born with a birth defect or had developed a childhood cancer. Sufficient NTDs, oral clefts, and childhood (diagnosis before age 20) leukemia/NHL were ascertained to move forward with a study of these adverse outcomes.

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 these potential cases. For oral clefts without medical records, funds were provided for a dental exam to confirm that surgery was performed as a result of a cleft lip or palate. A case-control sample was taken that included all the potential cases. A random sample was taken of those children included in the survey for whom a birth defect or childhood cancer was not reported. The control sample originally totaled 816, but this number was much more than was needed for a 1:10 ratio of confirmed cases to controls—it was obvious that some of the potential cases would not be confirmed. Efforts were made to contact both parents of 651 controls, and 548 (84.2%) were interviewed (for 87 of the controls, only the father could be interviewed).

Of the 35 reported NTD, 15 were confirmed (6 anencephaly, 9 spina bifida) and the parents of all 15 were interviewed; 13 were confirmed *not* to have the condition, 2 potential cases had no medical records for confirmation, the parents of 2 potential cases refused to participate, and three cases were ineligible (the mothers of two NTD cases did not live on base during their pregnancies and the other NTD was born in 1986). Of the 42 reported oral clefts, 24 were confirmed (11 cleft palate, 13 cleft lip with or without cleft palate) and the parents of 23 were interviewed; 11 reported oral clefts were confirmed *not* to have the condition; 4 potential cases had no medical records for confirmation, and the parents of 3 potential cases refused to participate. Of the 29 reported childhood leukemia/NHL, 13 were confirmed (11 leukemia, 2 NHL). The parents of all confirmed cases were interviewed; 8 reported leukemia/NHL were confirmed *not* to have the condition; 1 potential case had no medical records for confirmation; the parents of 3 cases refused to participate; and 4 cases were ineligible (one case was diagnosed with NHL at age 25, and the mothers of 3 cases were not on base during pregnancy). In total, 52 of the 106 reported cases were confirmed and the parents of 51 of these confirmed cases were interviewed.

The parental interviews obtained information on maternal residential history (up to 1 year of life of the child), water consumption, occupational history, whether either of the parents served in Vietnam, and other risk factors during pregnancy such as illnesses, medications, hobbies, alcohol consumption, and smoking.

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 study completion in mid-2009.

Methods

Several steps were necessary to determine the feasibility of conducting additional studies at Camp Lejeune. To ensure representation of the affected community (i.e., Marines and naval personnel assigned to the base, their families, and the civilians who worked at the base) in the deliberations concerning the feasibility of future studies at the base, a Camp Lejeune Community Assistance Panel (CAP) was established. The panel initially included seven members representing the affected community, two technical advisers from academia (an epidemiologist and a toxicologist) who had experience working with community groups on environmental issues to serve as resources for the CAP, an epidemiologist from the Navy and Marine Corps Public Health Center (NMCPHC), and a DoD representative. ATSDR staff also participated at CAP meetings. The first meeting occurred in February 2006, and the CAP has met quarterly since then. The purpose of the CAP was to involve fully the representatives of the affected community in the deliberations concerning the feasibility of future studies at the base and to provide the technical assistance necessary for their full participation in the deliberations. Subsequently, two community members resigned but were replaced with two additional community members, and the toxicologist, NMCPHC epidemiologist, and DoD representative stepped down; however, NMCPHC replaced the epidemiologist with another staff member.

The additional steps necessary to assess the feasibility of conducting additional studies at the base are described below.

First Step: Computerize Base Family Housing Occupancy Records

For the "SGA study," ATSDR computerized the approximately 90,000 base family housing occupancy records (for a description of these data, see Appendix I). The name of the occupant assigned to the housing, the street address, and the rank were entered for all records. The dates of residence were, however, only entered in the database for those records needed to assign exposures to the mothers of the births in the "SGA study." This meant that over 75,000 records were entered without including the dates of residence. To remedy this, ATSDR decided to computerize fully the data on the 90,000 records so that for all records dates of residence would be entered.

The family housing records are an important source of information for assigning drinking water exposures to those who resided in family housing. It was also possible that these records might be useful in identifying a cohort if the names of the occupants assigned to the housing could be linked with personnel data at the Defense Manpower Data Center (DMDC). In the process of computerizing the family housing records, ATSDR discovered that about 15,000 records were missing from ATSDR's storage area. A total of 74,980 records were computerized. ATSDR is considering recovering the lost records by printing out the names and addresses of the approximately 15,000 records from the original computerized file of 90,000 that were not entered in the new file and locating the corresponding hard copy records in the housing files in storage at the base.

Second Step: Assess Feasibility of Linking DMDC Personnel Data with Family Housing Data

The second step was to determine whether it was feasible to use the family housing database to identify a cohort for a future study. Data available from the family housing records (full name of the sponsor, rank, street address and dates of residence) were insufficient to link with adverse health outcome databases such as the CDC/NCHS National Death Index (NDI). Moreover, additional information would be necessary so that a locating firm could determine the current addresses of those assigned to family housing. Therefore it was important to determine whether the information from the housing records could be linked with personal identifier data (e.g., social security number (SSN) and date of birth) available from the DMDC personnel master file database.

ATSDR provided DMDC with data from the computerized family housing records for 11,810 occupants who were assigned family housing and who were parents of infants included in the "SGA study." Of those occupants, we had date of birth information on 9,291 (the parent's date of birth was obtained either from the child's birth certificate or from information obtained from the 1999–2002 telephone survey for the case-control study). DMDC was able to achieve a unique match with its personnel master file for about 65% of these 9,291. Next, DMDC attempted to match the 11,810 records to its personnel master file using only the information on the occupant's name, rank, and residence dates. Over 18,000 DMDC records matched the 11,810 housing records, indicating about 6,000 "false positives" or records without a unique match.

In summary, it was not feasible to link the housing occupant information (name, rank, and dates and location of residence) with the DMDC personnel database unless additional information such as date of birth was available. Because date of birth was available for fewer than 15% of the housing occupants, ATSDR concluded that it would not be feasible to use the family housing records to identify a cohort for future study. The family housing records would, however, continue to be valuable for assessing drinking water exposures to a cohort that included residents of base family housing.

Third Step: Assess Utility of DMDC Data for Identifying Cohort Members

To identify DMDC electronic databases that might be useful in identifying cohorts who lived or worked at the base during the period when the drinking water was contaminated, an ATSDR senior epidemiologist (Dr. Frank Bove), an epidemiologist from the Navy and Marine Corps Public Health Center (formerly Navy Environmental Health Center) (Dr. Chris Rennix) and an epidemiologist from Boston University School of Public Health (Dr. Richard Clapp, a technical adviser to the Camp Lejeune CAP) met with staff from the DMDC. DMDC staff provided data layouts for the active duty military personnel master file and the civilian personnel data file. The earliest date for the active duty file was June 1971, but the earliest date for which unit codes were available that could identify those active duty personnel stationed at Camp Lejeune was June 1975. The civilian file begins in December 1972 and includes the base location, but the employment start date is not available until June 1974.

Key data items in both files include: date of birth, SSN, race/ethnicity, sex, education level attained, and length of service (for a description of these datasets, see Appendix G). In the active duty file, only a partial last name is available prior to 1977, with full name available from 1977 onward. The civilian file does not include name until December 1981, with full name available from that date onward. The civilian file includes the occupation code and the location of occupation. The active duty file has the unit identification code indicating where the person was stationed. ATSDR requested that DMDC provide demographic data for the active duty and civilian personnel who were stationed at Camp Lejeune before 1986. These descriptive data were provided to ATSDR and are provided in the tables in Appendix E of this report.

Another DMDC database that might be useful for future studies is the Automated Central Tumor Registry System (ACTUR), which collects data from military treatment facilities on active duty personnel, retirees, and their dependents.

Fourth Step: Assess Feasibility of Using Other Databases to Identify Family Members

DMDC data were available to identify a cohort of active duty Marine and naval personnel who were stationed at the base anytime from June 1975 onward. DMDC data were also available to identify a cohort of civilian workers who were stationed at the base anytime from December 1972 onward. The Camp Lejeune Science Panel also recommended, however, that an attempt be made to identify cohorts of children and other family members who resided on base. The DMDC database "Defense Enrollment Eligibility Reporting System" (DEERS) has information on family members of active duty and retirees, but the database did not begin until near the end of the drinking water contamination period, September 1983. No other DMDC database appeared to be useful for identifying children or other family members.

ATSDR contacted the DOD Education Activity to identify any data the activity might have on children attending the base schools. Transcripts of the graduates of the Camp Lejeune high school were stored on microfilm data cartridges (with a metal core) and plastic reels. Information on students who were transferred from the base before graduation was also available on microfilm. The cartridges and plastic reels were stored at Fort Benning, GA. ATSDR evaluated the condition of these cartridges and plastic reels during a site visit to Ft. Benning. Pre-1980 data are stored on damaged cartridges. In fact, some of the cartridges are so damaged they cannot be used. Virtually all of the remaining cartridges are extremely fragile and must be carefully hand-reeled to avoid breaking the microfilm tape. The plastic reels contain data from 1980 onward and can be automatically reeled. The high school transcripts contain the student's name, address, date of birth, and sex. Some students have SSNs. The parent's name is also available. The microfilm information showed that during 1973–1984 the size of the graduating class ranged from 78 to 132. Because of damaged cartridges, information on the graduation class size could not be obtained for the years prior to 1973 and the graduating classes of 1973 and 1979.

The data on students who did not graduate from the high school include student name, address and date of birth but do not include parent's name. How many students are included in these tapes is not known. Cartridges containing pre-1974 data are damaged beyond use. Data for the 1978–79 school year also cannot be read.

ATSDR contacted the Camp Lejeune High School (LHS) alumni association to find out what information it might have for the over 3,500 registered former students and faculty/staff. The records are organized into two databases: an access database by graduation year (contains only self-reported email addresses, mailing addresses, and phone numbers, not all of which are current, and does not include the years the students attended LHS, where they lived on base, parent's name, or birth dates) and a Web site that contains email addresses of those who register. The earliest records date back to the class of 1945 (the year the school opened). In preparation for a reunion in 2010, the alumni association intends to organize their files for a mass mail out (to occur by summer 2008) to see how many of the addresses are current.

Because of the damaged cartridges and the incomplete data available from the alumni association, ATSDR concluded that the number of students that could be identified from these data sources was insufficient for a future study.

Fifth Step: Assess Feasibility of Using Specific Adverse Health Outcome Databases

A 1996 NAS report on the Health Consequences of Service During the Persian Gulf War (IOM 1996) concluded that

> The single most troublesome problem encountered in attempts to conduct epidemiologic studies of illnesses among Persian Gulf War veterans has been the inability to retrieve information on medical care events such as hospitalizations, outpatient visits, and diagnoses and treatments from the Department of Defense and the Department of Veterans Affairs medical records in a uniform and systematic manner.

The NAS report went on to say that: "Current systems are fragmented, disorganized, incomplete, and therefore poorly suited to support epidemiologic and health outcome studies." A 1998 GAO report (GAO 1998) reached similar conclusions: "None of the data sources that provide information on the health characteristics of Gulf War veterans can be used to reliably estimate the incidence of tumors. Existing federal and state data systems are generally limited by poor coverage of the Gulf War veteran population and problems of reporting accuracy and completeness."

In one sense, the challenge of ascertaining cancers and other diseases among cohorts who lived or worked at Camp Lejeune before 1986 is less challenging than the situation with the Persian Gulf veterans. With the Camp Lejeune cohorts, sufficient time has elapsed since date of first exposure to account for a latency period. Nevertheless, as with the Persian Gulf War veterans, over half remained in active duty service only 3 years, and over three-quarters left active duty after 5 years. This means that health databases that only follow military personnel while they are on active duty will not capture most of diseases that occur among the Lejeune cohorts. Moreover, most military personnel (and their family members) do not seek care at VA or DOD health facilities after they leave the service. That said, however, it may be feasible to use available DOD and VA health databases in future health studies if they are supplemented by other health databases and other sources of medical information.

ATSDR first explored the health databases available from the DOD (for a description of these databases, see Appendix J). An ATSDR senior epidemiologist (Dr. Frank Bove), an epidemiologist from the Navy and Marine Corps Public Health Center (formerly Navy Environmental Health Center) (Dr. Chris Rennix) and an epidemiologist from Boston University School of Public Health (Dr. Richard Clapp) who is a technical adviser to the Camp Lejeune CAP, met with staff from the Naval Health Research Center (NHRC) to discuss their database, “Career History Archival Medical and Personnel System” (CHAMPS). The CHAMPS system can be used to ascertain a disease requiring hospitalization among active duty personnel. A brief description of CHAMPS appears in Appendix J. The data on active duty Marines begins in 1980. ATSDR requested frequency data from CHAMPS on liver and kidney diseases among Marine and naval personnel, including those who were identified as stationed at Camp Lejeune. The focus was on kidney and liver diseases—these have been associated with occupational solvent exposures. The frequencies of liver and kidney cancers from 1980 to 2000 among the slightly more than 1 million active duty Marines were too few to conduct a study. Although also low in frequency, an evaluation of liver necrosis and nonalcoholic liver diseases may be possible. The frequencies of renal hypertension and kidney diseases (acute and chronic glomerulonephritis, nephrotic syndrome, nephritis, acute and chronic renal failure, renal sclerosis, and impaired renal function) were also of sufficient size to include in a study. The NHRC identified about 125,000 Marines in the database who were stationed at Lejeune at some time before 1986.

The DOD’s ACTUR was established in mid-1986. ACTUR is the DOD’s main cancer data collection and reporting system and covers hospitalizations of active duty personnel, retirees, and family members at military treatment facilities. The ACTUR is essentially a passive surveillance system; thus the completeness of reporting by the DOD treatment facilities is unknown. Nevertheless, if supplemented by other sources of cancer incidence data, this database may be useful in ascertaining and confirming cancer cases among cohorts who worked or resided at the base.

The U.S. Department of Veterans Affairs maintains databases that have been used for mortality and morbidity studies. The Beneficiary Identification and Record Locator Subsystem (BIRLS) Death File was created in 1970 as an extension of a manual Master Index of recipients of veterans benefits. In 1972, BIRLS completely replaced the Master Index. The BIRLS contains records of all VA beneficiaries, including veterans whose survivors have applied for a death benefit. Data fields in the BIRLS include the veteran’s name, SSN, periods of service, current address, date of birth, date and state of death, and location of the veteran’s hard copy file. The BIRLS does not have cause of death information other than whether the death was due to “natural” causes, combat, unknown, or “other.”

For date of death, the BIRLS has a high accuracy rate. Because of lack of information on cause of death and, even more important, an ascertainment rate of only about 80% for deaths occurring among the VA population, the BIRLS is not, however, an adequate source of mortality data by itself. Sohn et al. (2006) recommend supplementing the BIRLS with three other databases available from the VA to achieve 100% ascertainment: the Medical SAS Inpatient Datasets (also known as the Patient Treatment Files or PTF), the Social Security Administration Death Master File (SSA) and the Medicare Vital Status file for Medicare-enrolled veterans. The advantage of using all four of these databases to ascertain mortality compared to simply using the CDC/NCHS National Death Index (NDI) is that these data are free of charge to researchers affiliated with the VA and the data in the BIRLS, and the SSA are updated monthly. On the other hand, the NDI charges a fee-per-subject searched and has a reporting lag time of 12–24 months. Still, the key advantage of the NDI is that it contains information on the cause of death. Of the four databases available from the VA, only the PTF contains information that might be useful in determining cause of death; that is, the diagnosis that led to hospitalization and the condition that accounted for the majority of the hospital stay. Unfortunately, a study of the mortality ascertainment rate of the PTF for the VA population found that only 12% of the deaths were recorded in this database (Sohn et al. 2006).

The VA morbidity databases include the PTF (established in 1970), the Outpatient Care Files (established in 1996), and the Veterans Affairs Central Cancer Registry (VACCR). The VACCR was established in 1995 and aggregates the data collected by the tumor registries of the approximately 120 VA medical centers diagnosing or treating patients with cancer. In studies of Vietnam veterans, miscoding of discharge diagnoses in the PTF for certain types of cancers was found to be a serious problem. For example, about 40% of connective and other soft tissue cancers were misclassified in one case-control study of Vietnam veterans (GAO 1998; Kang et al. 1986). Presumably the VACCR has minimized these coding errors. The key problem with using the VA morbidity databases is the poor coverage of the veteran population. The 1992 National Survey of Veterans found that in 1992 only about 10% of veterans used some form of VA medical care. Another survey conducted by the VA in the late 1980s found that about 20% of veterans had ever used a VA hospital (GAO 1998). Most veterans are not eligible for VA care. Only persons with service-connected disabilities or who have low incomes can receive care.

Additional sources of mortality and morbidity data include the CDC/NCHS National Death Index (NDI), the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data, and state cancer registries (see Appendix J). The NDI has mortality information beginning in 1979. The "routine NDI" provides the death certificate number, state of death and date of death so that copies of the death certificate can be obtained from state health departments. "NDI Plus" has cause of death information beginning in 1979. The NDI is considered the gold standard for mortality ascertainment and covers the entire national population. State health departments are required to report death data to the NDI, so ascertainment is complete. A unique match is almost always (i.e., >95%) obtained with just the subject's SSN. The current fee for NDI Plus is $0.21 per subject per year searched.

SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of the U.S. population. Case ascertainment began in 1973 with the initial reporting areas being CT, IA, NM, UT, HI, the metropolitan areas of Detroit and San Francisco-Oakland, and Puerto Rico. Other areas and states were included in later years and some areas dropped out of the program for periods of time. The current SEER data cover 17 areas (Detroit, Seattle, Atlanta, rural GA, the Alaska Native Registry, and the states of CA (San Francisco, San Jose-Monterey, Los Angeles, and the rest of the state), CT, HI, IA, NM, UT, KY, LA, and NJ). State cancer registries or programs exist in every state but are of varying quality and coverage periods. Although some states have data beginning in 1979 or earlier, in 1990 at least 10 states did not have cancer registries (Izquierdo et al. 2000). All states have cancer data from 1997 onward. States also vary in the willingness to share data with researchers. Some registries have problems with duplicate reports and reporting delays. All that said, state registries still provide coverage of virtually the entire U.S. population.

Sixth Step: Assess the Feasibility of Determining Each Unit's Barrack Location

The assessment of drinking water exposures will be based on the extensive groundwater contaminant fate and transport and distribution system modeling of the Tarawa Terrace and Hadnot Point water systems. The modeling effort will be completed in 2009. The models provide monthly estimates of contamination levels in the contaminated systems. The water system serving each family housing area is also available. For those who were assigned to family housing, computerized records indicate the name of the person assigned to the housing unit, the street address, and dates of residence.

For those who lived in the bachelor officer's quarters or in barracks, the unit code (and unit description) assigned to that person must be linked to an area on base where the unit's barracks was located. Most of the barracks were located in areas served by the Hadnot Point system. No official source of information is, however, available that links units to barracks locations. Therefore, to identify those units and their barracks that were located in areas served by water systems other than Hadnot Point, a meeting was held at the base on February 13, 2008 with current base staff and retired Marines. Consensus was reached on the barracks locations for most units. Resolution of remaining issues and questions concerning the barracks locations of units should occur within a few months (see Appendix I for the issues requiring resolution). For a civilian worker, no official source of information links the occupation code and occupation description to the specific area on base where the work was performed. Information on the location of each occupation will be obtained from base staff (e.g., base industrial hygienists). Information on the length of service is available from the computerized personnel data.

Information on the drinking water systems serving each of the housing areas is provided in Appendix H. The data sources and variables that will be used to link the water systems to the cohorts' residences on base are described in Appendix I.

Summary

Data are available from the DMDC to identify a sufficiently large cohort of active duty Marine and naval personnel who were stationed at any time at Camp Lejeune from June 1975 onward. Data are also available to identify a cohort of civilian workers who were stationed at the base from December 1972 onward. The DMDC data includes SSN and date of birth, which can be used to link with health databases. Unfortunately, full name is not available for some of the years. Inclusion of participants in the 1999–2002 ATSDR survey in a future study is also possible. It is not feasible to use the family housing records to identify a cohort. These data are, however, valuable in assessing exposures to those cohort members who resided in family housing. Unfortunately, the high school transcript microfilm cartridges are in poor condition for most years up to 1980. Therefore, it is not feasible to use these data to identify a cohort.

Health databases are available that are feasible to use in future studies of Lejeune cohorts. The VA BIRLS, the Medicare Vital Status file, the SSA Death Master File, and the NDI can reliably determine vital status and cause of death. For cancer incidence, the DOD, NHRC, and VA databases are inadequate by themselves to ascertain cases occurring in the Lejeune cohorts. A national cancer database is nonexistent; therefore a study that relied solely on data linkages to ascertain cancers in the Camp Lejeune cohorts would have to use cancer registries in every (or almost every) state. The NHRC's CHAMPS database might be useful for ascertaining diseases other than cancers, (e.g., liver and kidney diseases). Yet this database is limited—it covers only hospitalizations occurring among those who are on active duty.

Literature Review of the Health Effects of the VOC-Contaminants

Studies of VOC-contaminated drinking water and adverse birth outcomes and childhood cancers were discussed above (see page 11).

Virtually all of the studies of the chronic human health effects of these chemicals are occupational studies. Medically confirmed adult cancers have been studied in only two populations (i.e., northern NJ and upper Cape Cod, MA) exposed to public drinking water contaminated with PCE (Aschengrau et al. 1993; Aschengrau et al. 1998; Paulu et al. 1999; Aschengrau et al. 2003; Fagliano et al. 1990; Cohn et al. 1994). Only one population (northern NJ) exposed to TCE-contaminated public water supplies has been studied for medically confirmed adult cancers (Fagliano et al. 1990; Cohn et al. 1994). No studies have been conducted of medically confirmed, noncancer adult diseases and exposures to solvent-contaminated public drinking water supplies. A neurobehavioral test battery was used in a study of a population exposed to solvent-contaminated public drinking water in Denver (Reif et al. 2003).

Given the high levels of VOC contaminants in the drinking water at Camp Lejeune and the lack of drinking water studies, an expert science panel convened by ATSDR in 2005 concluded that there was a need for studies of adult conditions, in particular causes of death and cancer incidence, among those exposed at the base.

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 & Jo 1996; WHO 2005). The northern NJ drinking water study included populations in 75 towns and evaluated TCE levels in municipal supplies 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).

The National Toxicology Program's 11th Report on Carcinogens has stated that "limited evidence" from human studies, "sufficient evidence" from animal studies (multiple sites or organs in multiple species), and "information that suggesting TCE acts through mechanisms that indicate it would likely cause cancer in humans," TCE is "reasonably anticipated to be a human carcinogen." The World Health Organization International Agency for Research on Cancer (IARC) classifies TCE as a probable (Group 2A) human carcinogen. ATSDR supported the NTP and IARC assessments, concluding that "cancer should be an effect of concern for people exposed to TCE in the environment." (Williams-Johnson et al. 2001). Virtually all of the epidemiological studies of TCE are occupational studies. These occupational studies are 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).

In 2006, the National Academy of Sciences/National Research Council, Committee on Human Health Risks of Trichloroethylene, issued its report entitled *Assessing the Human Health Risks of Trichloroethylene* (NAS/NRC 2006). For **lung cancer**, the NAS report concluded that

> 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 that

> 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, when liver and biliary cancers were combined, the standardized mortality ratio (SMRs) and SIRs for the "tier 1" cohort studies averaged to 1.1 and were not statistically significant (Wartenberg et al. 2000). For liver cancer only, one mortality study with an SMR of 1.7 (95% CI: 0.2-16.2) was based on four cases. The estimated average SIR for the 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) obtained a summary RR of 1.30 (95%CI: 1.09-1.55) for the subcohorts of workers identified within eight studies as more likely exposed to TCE. This estimate combined, however, liver and biliary cancers as well as mortality and incidence studies. When primary liver cancer was evaluated separately, a summary RR of 1.41 was obtained (95%CI: 1.06-1.87). Again, this summary RR combined mortality and incidence studies. The authors state that the findings for "European studies" (summary RR = 1.38; 95%CI: 1.13-1.67, for liver/biliary cancers) differed from the findings for "US studies" (summary RR = 0.97 for liver/biliary cancers). All four of the European studies were, however, incidence studies, and all four of the U.S. studies were mortality studies. In both meta-analyses, the summary RR for the mortality studies of liver/biliary cancers hovered around 1.0. Focusing on the cancer incidence findings, *both* meta-analyses found consistent associations between liver cancer incidence and TCE.

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 SMR for NHL mortality of 1.2 (95% CI: 0.9, 1.7) and 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 1.25 (95% CI: 0.87-1.79) for NHL mortality and 1.86 (95% CI: 1.27-2.71) for NHL incidence for studies that identified a specific TCE exposed subcohort. The meta-analysis concluded that there was "insufficient evidence to suggest a causal link between TCE exposure and NHL" despite the strong positive finding for NHL incidence. The authors emphasized the inconsistency among the studies on exposure-response trends, the lack of supportive toxicological evidence, and limited exposure assessments. 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 in the meta-analyses to be associated with TCE occupational exposures. 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, either large differences between males and females appeared 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.

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 two 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 six 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 seven 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, pancreas) were not found in the meta-analysis to be associated with TCE occupational exposure (Wartenberg et al. 2000).

In a small industrial plant producing small instruments, a cluster of three cases of **Parkinson's disease** was evaluated, together with 14 cases of Parkinsonism (Gash et al. 2008). 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. 2008). 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 & Goon 2008; Kamijima et al. 2007; Li et al. 2007; Nakajima et al. 2003). Within a few months of occupational exposure the skin rash occurs typically on the extremities, face, neck or trunk, and can reoccur after minimal reexposure. Some cases that did not use TCE but worked near the degreasing operations suggest that skin contact with TCE is not necessary (Kamijima et al. 2007).

Chronic occupational exposure to TCE has been associated with noncancer **liver disease** such as hepatic necrosis, fatty liver, and cirrhosis (NAS/NRC 2006). Some evidence in animal studies and occupational studies also suggests that TCE can cause noncancer **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" although it was unclear whether the effects were transient or permanent and whether they were relevant to humans (NAS/NRC 2006). Studies of spontaneous abortion and occupational TCE exposure have been inconclusive.

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.

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). In the last 7 years, a review of the epidemiological literature on PCE occupational exposures and cancers (Mundt et al. 2003) and two risk assessments for PCE in drinking water have been published (CA 2001; WHO 2006). In addition to these studies and reports, this assessment reviewed (but cannot cite) information from an April 2008 EPA draft toxicological review of PCE for external review only.

Two drinking water studies, one in Cape Cod, MA and one in 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; 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 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 pointed out that the epidemiological studies were conducted of dry cleaning workers who may have been exposed to other solvents including TCE, carbon tetrachloride, and Stoddard solvent. The report concluded, however, that "When all studies are considered, 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.

Excess mortality from **oral cancer** was found in one dry cleaner cohort (SMR=2.07; 95% CI :0.94-3.93) including five cases of cancer of the tongue among those employed 20 or more years prior to diagnosis (SMR=5.0; 95% CI: 1.62-11.68) but not in another dry cleaner cohort (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). One review concluded that 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, the evidence for an association between occupational exposures to PCE and oral cancer was "limited" and "unlikely" (Mundt et al. 2003).

Esophageal cancer was evaluated in four cohort studies (three studies of dry cleaners and one study of factory workers), and in three case-control studies where the exposure was employment in dry cleaning or laundry. The average SMR among the dry cleaning cohort studies was 2.2 (95% CI: 1.5-3.2) (Wartenberg et al. 2000). A study of laundry and dry cleaning workers combined found no association for the incidence of esophageal cancer, but an excess of esophageal cancer mortality was observed in the factory worker cohort (SMR=1.47; 95% CI:0.54-3.21) (Mundt et al. 2003). Although the case-control studies could adjust for potential confounders such as smoking and alcohol, these studies were severely limited by the small number of exposed cases and difficulties with exposure classification. 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).

Liver cancer was evaluated in five cohort studies (including two that combined laundry and dry cleaning workers and one that evaluated factory workers) and four case-control studies. Studies limited to dry cleaning workers observed no association with liver cancer. One study that combined dry cleaning and laundry workers found an elevated incidence among women (SIR=2.7; 95% CI: 1.5-4.5), and an excess was found in a case control study of male laundry workers (OR=2.50; 95% CI:1.02-6.14) (Mundt et al. 2003). A recent case-control study, however, 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). In one of these cohort studies, a statistically significant SMR was found only among those exposed to PCE and other solvents, not PCE alone (Mundt et al. 2003). One review concluded that an association between PCE and pancreatic cancer was "unlikely" because other solvents may have caused the observed excess in the one cohort study and because the cohort studies could not adjust for potential confounders such as smoking (Mundt et al. 2003). The average SMR across the cohort studies does, however, provide some evidence for a consistent and positive association. 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; 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).

Several cohort studies evaluated **lung cancer;** the average SMR for the cohort studies of dry cleaning workers 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).

Cervical cancer mortality was evaluated in several cohort studies of dry cleaning workers, and the average SMR across these studies was 1.7 (95% CI: 1.5-2.0); however, one cohort study that evaluated cervical cancer incidence found no excess (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). Despite the consistently positive findings, one review emphasized the lack of confounder adjustment in the cohort studies and the lack of exposure-response relationships to conclude that the available evidence is "inadequate" for a firm conclusion (Mundt et al. 2003). 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). The bladder cancer cases were too few 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. An excess of breast cancer was, however, 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; 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, however, observe frank **liver disease**, leading one review to conclude that no clear evidence supports an association with noncancer liver disease (WHO 2006).

Four studies of **kidney** biomarkers among dry cleaning workers obtained conflicting results (Ruder 2006). Yet 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 exposures) (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). In the same study, however, self-reported exposure to

PCE confirmed by expert review found no association with scleroderma. Moreover, 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 used a neurobehavioral test battery and found deficits ($p < .10$) 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 three cases born to exposed fathers and one case born to an exposed mother (Perrin et al. 2007). In a study of PCE-contaminated drinking water in eight 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 spontaneous abortion 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 spontaneous abortion where consistent findings of increased rates have been observed. Two studies found a reduced probability of pregnancy among exposed women (WHO 2006). Whether the spermatogenic effects would affect fertility is not known (WHO 2006).

In summary, given 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, and
- spontaneous abortions.

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 known human carcinogens. Because of a lack of studies, DCE is not classifiable as to its carcinogenicity. Similarly, no DCE exposure-chronic disease studies are available, either.

Occupational exposure to **vinyl chloride (VC)** is associated with liver angiosarcoma. In a pooled analysis of over 22,000 workers exposed to vinyl chloride, the SMR for liver cancer other than liver angiosarcoma was 1.35 (95% CI: 1.03-1.74) and excess mortality from soft tissue sarcoma was also observed (SMR=1.31; 95% CI: 0.63-2.41) (Bosetti et al. 2003). The researchers concluded that the slight excess in liver cancer was probably due to misclassification of liver angiosarcoma and the finding for soft tissue sarcoma was dismissed (Bosetti et al. 2003). Nevertheless, a meta-analysis of four worker studies obtained an overall SMR for soft tissue sarcoma 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 spontaneous abortion (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, due to inconsistent findings, small numbers of exposed cases, or the lack of sufficient studies, the evidence for the other diseases is less certain (HEI 2007).

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 U.S. EPA calculated 10^{-6} cancer risk for TCE, vinyl chloride and benzene are 3 ppb, 0.02 ppb, and 1 ppb, respectively. The lifetime health advisory exposure level for noncancer effects is 100 ppb for DCE and 10 ppb for PCE. Lifetime health advisory exposure levels have not been set for TCE, benzene, or vinyl chloride. The drinking water equivalent levels or DWELs—a lifetime exposure concentration protective of adverse, noncancer health effects that assumes all of the exposure to a contaminant is from drinking water—for TCE, PCE, DCE, vinyl chloride, and benzene, are 200 ppb, 500 ppb, 700 ppb, 100 ppb, and 100 ppb, respectively.

California has set carcinogenicity based (in animals or humans) public health goals (PHGs) for these contaminants, or in the case of DCE, noncancer endpoints (Web site: http://www.oehha.ca.gov/water/phg/allphgs.html). 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, noncancer endpoints, the CA goals 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).

Summary of Literature Review

Virtually all of the epidemiological studies of the VOC contaminants present in the drinking water at Camp Lejeune evaluated occupational exposures. Uncertainty remains about the relevance of these studies to drinking water exposures. In addition, uncertainty remains 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. As the panel of epidemiologists convened by ATSDR noted, while the average tour length for Marines is 3 years, many had shorter tours (see the minutes in Appendix A). 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 to address some of these uncertainties, future studies of mortality, cancer incidence, and noncancer diseases were worth conducting at Camp Lejeune.

Keeping in mind the caveats about the relevance of findings in occupational studies to drinking water exposures as well as the average Marine's tour of duty, the literature review has identified several cancers and other diseases that should be evaluated in future studies. These include

kidney cancers (TCE)

kidney diseases (TCE, PCE)

liver cancer and liver disease (TCE, VC) NHL (TCE, PCE, benzene)

leukemias (TCE, benzene, PCE) multiple myeloma (TCE, benzene)

cervical cancer (TCE, PCE) Hodgkin's disease (TCE)

bladder cancer (PCE) pancreatic cancer (PCE)

lung cancer (PCE, VC) esophageal cancer (PCE)

soft tissue sarcoma (VC) brain cancer (VC)

breast cancer (PCE)Parkinson's disease (TCE)

scleroderma (TCE, PCE)Lupus (TCE)

generalized skin disorders (TCE)spontaneous abortion (PCE, benzene)

aplastic anemia (benzene)

Criteria for Assessing the Feasibility of a Future Study

The mission of the Division of Health Studies within ATSDR is to promote responsive public health actions through generatation and communication of credible scientific information about the relationship between hazardous substances and adverse human health effects. Conducting epidemiological studies is one way to meet this mission. An epidemiological study may be proposed for a variety of reasons, including to

- focus on specific exposure-disease hypotheses with the primary goal of producing scientific knowledge that is generalizable to similar situations involving the particular exposures and diseases, and
- answer one or more specific questions a particular community might have concerning a possible link between hazardous substance exposures and the public health impact in that community.

Before the Division of Health Studies will recommend conducting a health study, several criteria must be examined and met. These criteria aid in determining the appropriateness of a health study, as such an activity is not indicated in all circumstances and settings.

The first criterion is "public health significance." A proposed study should be capable of producing findings that are generalizable to other populations with similar exposures. Additionally, those finding should inform, provide the basis for, or justify public health actions that can mitigate health risks. Given the exposures under study, the findings should be relevant to other communities, and the health outcomes evaluated should be biologically plausible. Chlorinated solvents such as TCE and PCE have been found in drinking water systems in many parts of the country and are of major public health concern. Specific causes of mortality and cancers have been linked to exposures to these contaminants in occupational studies and in the very few studies that have evaluated exposures to these contaminants in drinking water. Therefore, studies of mortality and cancer incidence at Camp Lejeune would have public health significance. Renewed concern about the health risks of TCE and PCE has also encouraged Congressional interest in the regulation of these contaminants in drinking water.

A second criterion is "scientific importance." A proposed study should be capable of providing new scientific knowledge or address key data gaps in our knowledge. A study may also promote new methodologies or important enhancements to existing methods. The historical reconstruction of contaminant levels in the drinking water systems at the base has already promoted important enhancements to the modeling of the fate and transport of contaminants in groundwater and assessing uncertainty in these models. These methods will be applicable to other groundwater contamination situations. Currently, serious gaps hinder the advancement of the scientific knowledge concerning the health effects of exposures to drinking water contaminated with chlorinated solvents. Few epidemiological studies have been conducted to evaluate the effects of these exposures. A mortality study and a cancer incidence study at Camp Lejeune could make a major contribution to the scientific knowledge on the health effects of these exposures.

A third criterion is "the ability to provide definitive results." A proposed study should be capable of minimizing biases and have sufficient statistical power to detect the effect sizes that are expected given the exposure situation. A major limitation of environmental and occupational studies is exposure misclassification bias that can produce a distortion of the exposure–response relationship, often to a bias towards the null or underestimation of the effect of an exposure. Other biases can occur from errors in disease classification, bias in the selection of study subjects and their follow-up, and biases due to confounding by other risk factors and by the "healthy veteran/worker effect."

To meet these criteria, a proposed epidemiological study should also

- Minimize bias in the selection of individuals into the cohort(s).
- Minimize bias in the health information obtained for each cohort member.
- Minimize bias due to risk factors other than drinking water exposures.
- Minimize bias in the assessment of exposures.
- Ensure sufficient statistical power to detect small excesses in disease rates.

Findings

Cohorts

Three possible cohorts have been identified that could be included in future studies (see Appendix G). Two cohorts can be identified using the DMDC personnel databases. These databases contain personal identifier information such as name, SSN, date of birth, sex, race/ethnicity, as well as information on dates and locations stationed or worked at the base. For active duty personnel and civilian workers, this information is available starting in June 1975 and December 1972, respectively. A third cohort could be identified from the participants of the 1999–2002 ATSDR Camp Lejeune survey conducted as part of the case-control study of specific birth defects and childhood cancers. This database has the names, dates of birth, and contact information at the time of the survey for parents who resided at the base anytime during a pregnancy that resulted in a live birth occurring between 1968 and 1985. Finally, a fourth source of future study participants could be those who complete the Navy/USMC health survey that will be mailed to all persons identified as civilian workers at the base, or who resided in family housing or barracks served by the Tarawa Terrace water system or the Hadnot Point water system during the periods when these systems were contaminated with VOCs. The Navy/USMC health survey was mandated by an act signed into law on January 28, 2008.

"DMDC-Identified Active Duty Cohort"

The DMDC personnel database contains unit codes that identify Marines and naval personnel who were stationed at the base. These unit codes were first computerized in June 1975. Using the personnel database, the DMDC identified 210,222 Marines and naval personnel who were stationed at any time at Camp Lejeune during the period June 1975 to December 1985. This latter date was chosen as the latest date for a cohort member to begin his or her active duty at the base to ensure that everyone had the potential of at least 1 year of exposure to the drinking water contaminants. All of the heavily contaminated wells at Camp Lejeune were shut down in February 1985, but based on the water modeling results, low levels of contamination continued at Tarawa Terrace through February 1987—water modeling of the Hadnot Point system is ongoing.

The following data items are available for this cohort: partial last name (1975–1976) or full name (starting in 1977), SSN, date of birth, sex, race/ethnicity, years of active duty, dates of service, unit code, marital status, number of dependents, education level attained, pay grade, and home of record.

Of the 210,222 full or partial names, 94.6% are Marines, 96% are male, 73% are "white", 4% are Hispanic, about 66% were born between 1953 and 1962, about 21% were born between 1963 and 1968, and 73 % were single. By 1985, nearly 80% had less than four years of active duty service. Detailed demographic information is presented in the Appendix E.

"DMDC-identified civilian occupational cohort"

DMDC personnel data on civilian workers contains the occupational code and the location of occupation beginning in December 1972. DMDC identified 8,085 civilians who worked at the base anytime during December 1972 to December 1985. The following data items are available for this cohort: full name (starting in December 1981), SSN, date of birth, sex, race/ethnicity, years of service, dates of service, marital status, number of dependents, education level attained, pay grade, home of record, occupational code, and location of occupation.

Almost 46% of the cohort are women, 76.5% are "white", about 50% were born after 1942, and as of 1985, 35% had 10 or more years of service while 32% had less than one year of service. About 17% were involved in training, slightly over 3% were firefighters, and about 33% were involved in "blue collar" occupations such as construction work, maintenance work, and custodial work. Detailed demographic information is presented in the Appendix F.

ATSDR 1999–2002 Survey Cohort

As part of the case-control study of specific birth defects and childhood cancers, a telephone survey was conducted from September 1999 to January 2002. Parents who resided on base anytime during a pregnancy that resulted in a birth between 1968 and 1985 were eligible. The parents of 12,598 births participated in the survey. The survey obtained the names, address at the time of the survey, dates of birth of the parents, the dates the parents were at the base, and the on-base family housing unit where they lived. The database includes about 4,100 Marines and naval personnel who left the base before June 1975 and would therefore not be included in the DMDC-identified active duty cohort. Moreover, the database contains about 12,000 spouses of military personnel.

Other Cohorts

ATSDR evaluated whether the Camp Lejeune family housing occupancy records could be used to identify an additional cohort. Data available from the family housing occupancy records (full name of the sponsor, rank, street address and dates of residence) are insufficient to link with adverse health outcome databases such as the NDI or for use by a locator firm to obtain current address. Therefore, it is necessary to link these records to the DMDC personnel master file database to obtain key personal identifiers such as SSN and date of birth. DMDC staff attempted to match the family housing records to the DMDC personnel master file database, but for over half of the family housing records could not obtain unique matches. Given this poor success rate, ATSDR concluded that the family housing occupancy records could not be used to identify a cohort. These data, however, remain important for verifying address and dates of residence for those who resided in the onbase family housing units.

ATSDR also evaluated whether a cohort of school children could be identified. The DOD Education Activity stores on microfilm cartridges and plastic reels the transcripts of students who attended the Camp Lejeune High School from the late 1940s onward. ATSDR inspected the current condition of the microfilm cartridges and reels in May 2007 and found that most of the microfilm tape cartridges containing information on students who attended the high school prior to 1980 were in unusable condition. Because of the damaged tapes, ATSDR concluded that it was not feasible to assemble a cohort of school children. No other databases were discovered that could identify other cohorts exposed to contaminated drinking water at the base. Another source of future study participants, however, could be those who complete the Navy/USMC health survey.

Health Databases

Mortality

As stated, the NDI is considered the “gold standard” for mortality determination and contains data from 1979 onward. The NDI Plus contains the International Classification of Diseases (ICD) codes for the underlying and multiple (“contributing”) causes of death from 1979 onward, but up to a 2-year lag occurs indeath reporting. The NDI covers the entire U.S. population as well as Puerto Rico and the Virgin Islands. Information required to link with the NDI data includes one or more of the following:

- SSN,
- exact month and ±1 year of birth, first and last name,
- exact month and ±1 year of birth, first and middle initials, last name,
- exact month and day of birth, first and last name,
- exact month and day of birth, first and middle initials, last name,
- exact month and year of birth, first name, father's surname,
- if the subject is female: exact month and year of birth, first name, last name and father's surname.

A unique match is almost always (i.e., >95%) obtained with just the subject's SSN. The current fee for NDI (and NDI Plus) is $0.21 per subject per year searched.

Although the "gold standard," NDI does not cover deaths occurring to those living outside the United States, Puerto Rico, and the Virgin Islands. The Social Security Administration's (SSA's) Death Master File (DMF) contains information on deaths occurring in other countries. The DMF is extracted on a quarterly basis from the SSA's master file containing personal identifier information for each person assigned an SSN. Information in the DMF includes name, SSN, last known residence, and the dates of birth and death. The primary sources of death information are relatives, funeral directors, financial institutions, postal authorities, and other governmental agencies. In addition to identifying deaths in other countries, the DMF can also determine vital status for the most recent 2 years, (i.e., during the NDI's 2-year reporting lag period). The DMF requires full name, date of birth, SSN, and sex.

In 1994, the SSA was authorized to release to health researchers vital status data for living subjects as well as for decedents (Doody and Chimes 2000; Cowper et al. 2002). Using several databases, SSA categorizes each person into one of four categories:

1. deceased (state of residence at death and date of death);
2. presumed living (based on earnings reported to IRS, contributions to SSA through payroll deductions, and benefits being received);
3. status unknown; and
4. failed SSN/invalid SSN.

This service can provide vital status information for those alive since the base opened in the early 1940s (Doody and Chimes 2000). Descriptions of both the NDI and SSA databases are provided in Appendix J.

A possibly more cost-efficient alternative to NDI is the database in the Veterans Affairs (VA) Beneficiary Identification and Record Locator Subsystem (BIRLS) death file, the Medicare Vital Status file, and the Social Security Administration (SSA) Death Master File. An efficient algorithm using these databases can achieve sensitivity (percentage of deaths identified or false negatives) and specificity (percent of those living not identified as dead or false positives) levels equivalent to using the NDI (Sohn et al. 2006). The identified deaths can then be sent to the NDI for cause of death information.

Cancer Incidence

The databases possibly available for cancer determination are described in Appendix J.

Two DOD databases could be used to identify and confirm those diagnosed with a cancer. Yet both have severe limitations. The ACTUR, which is operated by the Armed Forces Institute of Pathology, was established in mid-1986 to serve as the DOD's main cancer data collection, clinical tracking, and reporting system (Yamane 2006). The registry covers hospitalizations at military treatment facilities of active duty personnel, as well as other eligible beneficiaries of the Military Health System, (e.g., family members of active duty personnel and military retirees). The ACTUR is essentially a passive surveillance system. Although required by formal policies, the extent to which incident cancer cases are reported by healthcare staff and captured in the registry is unknown (Yamane 2006). The NHRC's CHAMPS database has data on cancers resulting in hospitalizations occurring among active duty personnel while on active duty. The Marine Corps data on begins in 1980. ATSDR requested the frequencies of hospitalizations for liver and kidney cancers during the period 1980–2000 for all Marines stationed at Camp Lejeune before 1986. Among the approximately 126,000 Marines identified as stationed at Camp Lejeune before 1986, three liver cancers and six kidney cancers were identified. The extremely low frequencies of these cancers in the database indicate that CHAMPS cannot be used as a primary source for the determination of cancer incidence.

The U.S. Department of Veterans Affairs established the VACCR in 1995 and aggregates the data collected by the tumor registries of the approximately 120 VA medical centers diagnosing or treating patients with cancer (Nahleh et al. 2007). The key problem with using this database, as with other VA databases, is its poor coverage of the veteran population. The 1992 National Survey of Veterans found that about 10% of veterans used some form of VA medical care in 1992. Another survey conducted by the VA in the late 1980s found that about 20% of veterans had ever used a VA hospital (GAO 1998). Most veterans are not eligible for VA care. As stated, only those with service-connected disabilities or who have low incomes can receive care.

National programs for cancer surveillance, such as SEER and CDC's National Program of Cancer Registries, maintain aggregated data on cancer incidence (e.g., by sex, age, race/ethnicity) that are useful for comparison rates. Because personal identifiers are not available, these systems cannot be used for case determination. To determine cancer cases, individual state cancer registries must be used. About ⅔ of state cancer registries have pre-1990 population-based data available. About ¼ of state cancer registries began collecting population-based data in the mid-1990s. At least 80% of the states have better than 90% completeness of determination(NAS 2000; ATSDR/DHS, no date). A pilot study of cancer incidence among Gulf War veterans matched these veterans and non-Gulf War veterans with data from the cancer registries in six states (CA, FL, NJ, TX, VA, and MD) and the Washington DC cancer registry (Kang 2005). The researchers found that 1) a state will grant access to its registry to legitimate academic/government researchers with appropriate credentials and justification of need after its IRB review, and 2) computer matching algorithms used in the project can identify incident cancer cases among these 1.4 million veterans.

The Gulf War cancer incidence study plans to use data from up to 12 state cancer registries to ascertain cancer cases among these veterans.

A NIOSH study published in 2003 used nine state cancer registries to determine cases of breast cancer in an occupational cohort of women exposed to ethylene oxide (Steenland et al. 2003). This study also mailed detailed questionnaires to cohort members as another method of case determination. Although medical record verification was sought for self-reported breast cancers, self-reported cases were included in the analyses even if medical records could not be found to verify them. A total of three mailings, including a postcard reminder, and follow-up phone calls were conducted to increase the questionnaire response rate. Completed interviews were obtained from 68% of the cohort (Steenland et al. 2003).

Other Disease Endpoints

In addition to mortality and cancer incidence, the Camp Lejeune Science Panel encouraged ATSDR to evaluate the feasibility of studying other disease endpoints. The U.S. Department of Veterans Affairs maintains the Patient Treatment Files (PTF), now also known as the Medical SAS Inpatient Datasets. Established in 1970, the PTF contains information on the diagnosis that led to a hospitalization and the condition that accounted for the majority of the hospital stay. The key problem for this—as with other VA databases—is that most veterans are not eligible for VA care and therefore using the PTF would not identify most cases of a particular disease among the Lejeune cohorts .

The NHRC's CHAMPS database contains data on hospitalizations occurring to those on active duty. For active duty Marines, the data begins in 1980. ATSDR requested the frequencies in the CHAMPS database for liver and kidney diseases that in at least one study have been associated with occupational solvent exposures. Among the approximately 126,000 Marines identified as stationed at Camp Lejeune before 1986, 19 cases of hypertensive renal disease were reported, as were 102 cases of other kidney diseases (acute and chronic glomerulonephritis, nephrotic syndrome, nephritis, chronic renal failure, and other disorders resulting from impaired renal function), 9 cases of liver disease without mention of alcohol, and 3 cases of liver necrosis. Although the frequencies of hypertensive renal disease and liver diseases are very low, it may be possible to conduct a study of these diseases. For the other kidney diseases, it would be worthwhile to focus on a subset of the diagnoses that have the greatest biological plausibility.

In addition to the PTF, CHAMPS, and state or federal data for cancers, causes of death, and adverse birth outcomes (i.e., birth weight, preterm birth, and birth defects), no computerized databases are available at the state or national level for other diseases.

Conclusions

After a review of available databases, ATSDR concludes that it is feasible to conduct a mortality study and a cancer incidence study of persons who lived or worked at Camp Lejune during the years in which drinking water was contaminated. These adverse health outcomes were biologically plausible given the high contamination levels of solvents found in the Camp Lejeune drinking water. These studies are also feasible because there is sufficient information to assess monthly drinking water exposures on base and because there are cohorts of sufficient size that can be identified and included in these studies.

All-Causes Mortality Study

The mortality study would evaluate all causes of death, including cancers and noncancer diseases among: 1) those members of the cohort of 210,222 Marines and naval personnel who began active duty service anytime during the period June 1975 and December 1985, 2) those members of the cohort of 8,085 civilians who began DOD employment anytime during the period June 1974 and December 1985, and 3) a sample of 50,000 Marines and 5,000 civilians stationed at Camp Pendleton anytime during 1975–1985 who started duty on or after June 1975 and who never were stationed at Camp Lejeune during the period of drinking water contamination. The definitions of the cohorts are based on the availability of duty location data. The DMDC personnel databases can provide complete information on duty locations only for those active duty members and civilian workers who began service on or after June 1975 and on or after June 1974, respectively.

To improve the credibility of the mortality study, the panel of epidemiologists convened by ATSDR recommended that the study include an external, unexposed comparison group, similar in all respects to the Marines and civilian workers at Camp Lejeune except for exposure to VOC-contaminated drinking water. The inclusion of the Camp Pendleton samples would address two major issues: 1) inadequate statistical power in the internal comparisons due to small numbers who are unexposed within the Camp Lejeune cohorts, and 2) doubts that have been raised concerning whether anyone was unexposed to contaminated drinking water at the base (e.g., because of water consumption during field training and the use of Hadnot Point water to resupply the Holcomb Boulevard system during summer months when the golf courses were irrigated).

It is not feasible to include the parents who participated in the 1999–2002 ATSDR survey in the mortality study unless they are already included in either the active duty cohort or the civilian cohort. Because survey participants had to be alive at the time of the survey, it would not be useful to include them in a mortality study. The follow-up period when they would be at risk of death is short (i.e., from the date of the survey interview to the year 2006). Moreover, inclusion of this group in the mortality study might introduce a bias—they represent a "survivor population" whose mortality experience might differ substantially from the two other cohorts.

To determine vital status, one of two approaches would be used: 1) a customized algorithm that efficiently utilizes VA, Medicare, and SSA databases, or 2) using the NDI and SSA databases. The most cost-efficient approach may be to employ, in a customized algorithm, the data in the VA BIRLS death file, the Medicare Vital Status file, and the Social Security Administration (SSA) Death Master File to determine vital status and then send the information on the persons who have died to the NDI for cause of death information. The VA and SSA may allow these data to be used free of charge. Alternatively, both the SSA database and the NDI could be used to determine the vital status of the cohort members. Both the SSA and NDI are necessary to determine vital status: the NDI is limited to deaths occurring in the U.S., Puerto Rico, and the Virgin Islands, whereas the SSA databases can identify deaths occurring in foreign countries. The cost of an NDI search is $0.21 per person per year. Because the size of the cohorts, including the Pendleton samples, is roughly 225,000 and the follow-up period is about 30 years, the cost of the NDI search would be approximately $1.5 million.

To determine vital status, the key personal identifiers are SSN, date of birth, and sex. These data items are available for both cohorts. Another key data item, full name, is not available for these cohorts during some of the years. Successful data linkage with the VA, Medicare, NDI and SSA databases can, however, be accomplished without full name.

The NDI-Plus would be used to obtain the causes of death for deaths occurring from 1979 onward. The NDI-Plus currently provides the ICD-9 codes for the underlying and multiple ("contributing") causes of death for the years 1979–2006. (Data for 2007 should be available by mid-2009) Although studies show that discrepancies between death certificate information and information provided by the NDI-Plus are minimal (Sathiakumer et al. 1998), death certificates will be obtained from state health departments to confirm causes of death of specific interest. For deaths occurring before 1979, a nosologist will code the cause of death from the death certificate.

The active duty and civilian worker cohorts would be analyzed separately. Follow up would begin in at the start of known assignment at Camp Lejeune (i.e., based on the computerized unit code for active duty Marines and naval personnel or the occupation location code for civilians) or start of active duty for the Camp Pendleton cohort, and continue to the end of the study period, December 31, 2007, or to the date of death. For those not identified as dead but identified as either "Status Unknown" or "Failed SSN/invalid SSN" in the SSA database, follow-up time would accrue until the date of the person's last known vital status.

For those who resided in family housing units or barracks served by the Hadnot Point or Tarawa Terrace drinking water systems, exposure would be based on the monthly levels of contaminants during the period when they were on base. Those who resided in family housing or barracks served by other water systems at the base would be assumed as unexposed to drinking water contamination. Exposures may be lagged in the analyses to account for a latency period.

The active duty cohort and the cohort of civilian employees would be analyzed separately. Initially, SMRs would be calculated comparing the cause-specific mortality rates in each cohort with national rates. Such comparisons may, however, be affected by bias due to a "healthy veteran effect." This bias is caused by differences in underlying mortality rates between veterans and the general public. Bias due to the healthy veteran effect has been observed in studies of Vietnam veterans and Gulf War veterans. For example, all cause mortality among Vietnam veterans was significantly lower than the U.S. population, and cancer mortality rates were also lower (Boehmer et al. 2004; Dalager et al. 1997). All cause mortality and cancer mortality were also lower among Gulf War veterans (Kang et al. 2001). One method to minimize this bias is to compute standardized mortality odds ratios (SMORs). The SMOR can be computed in a manner that is less prone to the healthy veteran effect by using as "controls" those causes of death that 1) are expected to be unrelated to drinking water exposures and 2) have a similar healthy veteran effect bias as the "case" cause of death (Checkoway et al. 2004).

Still, the primary method to minimize bias due to the healthy veteran effect would be to conduct internal comparisons between those exposed to contaminated drinking water and those unexposed, as well as internal comparisons among exposures to different levels of drinking water contaminants. One possible problem in conducting these internal comparisons may be that the unexposed group will be too small for adequate effect-estimate precision and statistical power. Therefore, comparisons would be made between the Camp Lejeune cohorts and the sampled Marines and civilian workers taken from Camp Pendleton.

For comparisons with national rates, the mortality study should have sufficient statistical power to detect moderate increases in risk for most cancers. For other causes of death that are more frequent, there will be sufficient statistical power to detect small increases in risk (see Appendix B).

Information on smoking and alcohol consumption, occupational history, and other potential risk factors are not available from the computerized databases that will be used in the mortality study. To take these potential confounders into account, one of two strategies can be considered:

1. Information from the Navy/USMC health survey could be used if the survey has a satisfactory participation rate (i.e., ≥ 65%). Surveys would be sent to everyone in the mortality study and to next-of-kin of those who have died. Similar to a "two-stage sample," information on exposure and vital status will be available for everyone in the study who are not lost to follow up, but information on smoking and other risk factors will be available only for those who complete the health survey. Nevertheless, information from the health survey participants can be used to adjust for confounding in the analyses of the entire study population (Schaubel et al. 1997; Collet et al. 1998).
2. If the Navy/USMC health survey does not achieve at least a 65% participation rate, nested case-control samples with next-of-kin interviews could be conducted for those causes of death that are known or suspected of being associated with drinking water or occupational exposures to VOCs. Controls would be randomly sampled from causes of death that are not of interest. Next of kin is listed on the death certificate. Next of kin interviews would obtain detailed information on activities and residences at the base, occupational histories, and information on other risk factors.

Cancer Incidence Study

Many cancers are not fatal and have a long survival time. This is true of some of the specific cancers that have been related to occupational or drinking water exposures to PCE or TCE such as kidney cancer, non-Hodgkin's lymphoma, bladder cancer, leukemia, and breast cancer. Evaluating the incidence of these cancers will result in higher expected numbers of cases, and therefore higher statistical power—or the ability to detect lower meaningful risks—than the evaluation of mortality rates.[2] In addition, because of small numbers, insufficient statistical power may be available to evaluate breast cancer mortality. Most likely, sufficient statistical power will be available to evaluate breast cancer incidence.

This study would utilize two approaches: 1) data linkages, and 2) the Navy/USMC health survey. For the data linkage approach to be successful, it would be necessary to gain either the participation of all 50 state cancer registries or the registries in the states where a sizeable percentage of Marine retirees reside (e.g., the first 25–30 states listed in Appendix C). If the data linkage approach is not successful, the cancer incidence study would be based solely on the health survey. On the other hand, if the health survey is unsuccessful, the cancer incidence study would be based solely on the data linkage approach. For the health survey to be successful, a participation rate of at least 65% is necessary. Methods such as repeat mailings and phone contacts would be employed to increase survey participation. If both approaches are successful, they could be combined.

1. *Data Linkage Approach*

The cohorts evaluated in the mortality study would be included in this study (including the samples from Camp Pendleton). The minimum standardized incidence ratios (SIRs) for comparisons between the active duty cohort and the U.S. population are presented in Appendix B. Because the number of women in the active duty cohort is small (i.e., approximately 8,000), statistical power to detect female cancers is not high. Therefore, ATSDR would add to the active duty cohort about 2,900 women who responded to the ATSDR 1999–2002 survey of parents of children who were carried or conceived at Camp Lejeune during 1968–1985 *and* 1) first resided at the base between 1975 and 1985 and 2) provided ATSDR with their SSNs.

This approach would match each cohort member's personal identifier information (i.e., name, SSN, and date of birth) to the available data on cancers from all 50 state cancer registries (or at least the first 25–30 cancer registries listed in Appendix C), the VA and DOD cancer registries (VACCR, ACTUR), the NHRC's CHAMPS, death certificates, and the NDI. Appendix J describes these cancer information sources. All state cancer registries have data available from 1997 onward. Therefore comparisons (SIRs and standardized incidence odds ratios) can be made between national cancer rates and cancer rates among the Lejeune and Pendleton cohorts for the period 1997–2007. Comparisons internal to the Lejeune cohorts (i.e., between exposed and unexposed), and comparisons between Camp Lejeune and Camp Pendleton, would use all cancers identified during the entire 1975–2007study period. Each cancer registry would be requested to match the cohort members' personal identifier information to the registry's data from the start of each registry's operation or 1975, whichever is later, to December 31, 2007 (i.e., the latest year in which complete data will be available from all the registries if data

[2] To illustrate the statistical power advantage of evaluating cancer incidence compared to cancer mortality, Appendix B provides a table of minimum detectable SIRs for specific cancers, assuming complete determination of cancer cases among the DMDC-identified active duty cohort, with a type 1 error rate of .10 and a type 2 error rate of 0.10. The minimum detectable SIRs can be compared to the minimum detectable SMRs in Appendix B.

collection begins in mid-2009, assuming that the registries have a reporting lag of 18 months). The registries would provide tumor characteristics and date of diagnosis. Cancer deaths identified from the mortality study would also be included in the study.

Because most of the cancer registries do not cover the entire study period, some cancers would be missed. Still, the cohort members were very young at the start of follow up, so the number of missed cancers would be low. In addition, bias due to missed cases would be minimal for the internal comparisons; there should be no relation between exposure status and the states where cohort members reside after retiring from service. On the other hand, the comparison between Camp Lejeune and Camp Pendleton could be affected by such a bias if differences appear between the two bases in the percentage of retired Marines migrating to states with older cancer registries. Although residences after retirement are not available from the DOD databases, it is possible to compare the home state frequencies of Marines stationed at the two bases to determine any significant geographical differences.

2. *Combined Data-Linkage and Health Survey Approach*

If the Navy/USMC health survey achieves at least a 65% participation rate, then the cancer incidence study would include those who complete the survey as well as all who are included in the data linkage approach. The personal identifier information for the health survey participant would be matched to the available data on cancers from all 50 state cancer registries and the federal (DOD and VA) cancer registries. Cancers identified in the mortality study would be included, and the next of kin listed on the death certificate would be sent a health survey to collect risk factor information on the deceased case.

The health survey will be mailed to the active duty and civilian cohorts, the Camp Pendleton sample, the 12,598 respondents in the 1999–2002 ATSDR survey, and anyone who has registered with the USMC or provided contact information to ATSDR. The health survey will collect information on any cancer a person may have had that was diagnosed by a health provider: the type of cancer, the date of diagnosis, and the state and hospital of diagnosis (to facilitate the acquisition of cancer registry data or medical record confirmation). Self-reported cancers will be confirmed by medical records or cancer registrations. 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. Other items in the survey will include a residential history, residences at the base, an occupational history, and information on several risk factors (e.g., SES, demographics, smoking, alcohol consumption).

In effect, this would be a "two-stage" approach in which information on exposures and cancers would be available for everyone in the study who is not lost to follow up, but information on potential confounders such as occupational exposures and smoking would be available only for those who complete the health survey. Nevertheless, information on potential confounders from those who complete the health survey could be used to adjust for confounding in the analyses of the entire study population.

To determine the most cost-effective method to enhance participation in the health survey, the survey will be mailed to a small sample of the Camp Lejeune and Camp Pendleton cohorts. Various methods to convert non-respondents will be tested to determine their cost-effectiveness: repeat mailings, phone contacts, incentives, and an introductory letter encouraging participation signed by the Commandant of the Marine Corps. The effectiveness of using a mixed mode approach (mailed survey and a Web-based survey) will also be evaluated.

Other options for future studies

In addition to a mortality and cancer incidence study, the Science Panel convened by ATSDR in 2005 suggested that nonfatal, noncancer diseases be considered for study. ATSDR has identified three possible approaches: 1) using the Navy/USMC health survey to identify diseases that can be confirmed by medical records, 2) use of the CHAMPS database to identify and confirm diseases, and 3) including questions in the Navy/USMC health survey on conditions that are unlikely or cannot be confirmed.

1. *Health survey of nonfatal, noncancer diseases*

The health survey will include questions on diseases that can be confirmed by medical records and are known or suspected of being related to solvent exposures: Parkinson's disease, severe kidney and liver diseases, lupus, scleroderma, and severe skin diseases. To be credible, the health survey must achieve at least a 65% participation rate. Medical records will be used to confirm the disease reports.

2. *Use of CHAMPS database to study nonfatal, noncancer diseases*

If the health survey does not achieve at least a 65% participation rate, then it might be feasible to study specific nonfatal, noncancer diseases that have been associated with occupational solvent exposures by utilizing the NHRC's CHAMPS database. This approach would, however, have severe limitations. The CHAMPS database includes diseases that are diagnosed among Marine and naval personnel *only while they are on active duty*, and the data only go back to 1980. **Because the use of the CHAMPS database for a study of nonfatal, noncancer diseases would likely have insufficient statistical power, ATSDR considers such a study to have a *very low priority***.

Because the CHAMPS data are already serially linked to DMDC personnel information, it would be possible to construct a service history for each Marine in the database. Yet the DMDC personnel database on Marines only began in June 1975. Thus service history before that date would not be available in a computerized dataset. For those stationed at Camp Lejeune, exposure can be assessed by linking the unit code to a particular barracks or, if the Marine lived in family housing, linking the Marine to the family housing records using full name, rank and dates of service.

In the CHAMPS database, 126,015 Marines who were stationed at Camp Lejeune before 1986 were identified. Among this group, there were19 cases of renal hypertension, 102 cases of all other kidney diseases, 9 cases of nonalcohol related liver disease, and 3 cases of liver necrosis. Other Marines who were on active duty before 1986 but not stationed at Lejeune could be identified in this database, and their liver and kidney disease rates can be obtained. Comparisons of disease rates between Marines stationed at Camp Lejeune and Marines stationed elsewhere could be conducted. In addition, a nested case-control sample with interviews could be conducted of all these Marines (i.e., those stationed at Camp Lejeune and those stationed elsewhere). Cases would be the specific diseases of interest among all the Marines, and controls could be sampled from all other diseases in the CHAMPS database that occurred among all the Marines. Interviews would be conducted of cases and controls to obtain risk factor information

Because of the limitations of the CHAMPS database, statistical power will be low for most of the diseases of interest. A case-control (1:1) sample of "all other kidney diseases" would have sufficient statistical power to detect a minimum odds ratio of 1.7. For renal hypertension, liver necrosis, and non-alcoholic liver disease, however, even a 1:8 case-control sample would provide inadequate statistical power to detect moderate effects, and only odds ratios between 2.75 and 3.5 would be detectable with 80% power.

3. *Including conditions in the health survey that cannot be confirmed by medical records*

If the Navy/USMC health survey achieves at least a 65% participation rate, then this approach is feasible. Questions on conditions that are known or suspected of being related to solvent exposure could be included in the survey regardless of whether they can be confirmed by medical records, (e.g., spontaneous abortion and skin rashes). The survey will include an open-ended question asking about any other condition(s) the participant wants to report.

The self-reported conditions can be tabulated, and if there appears to be a high response for a particular condition that is either suspected or known to be associated with solvent exposure, ATSDR would evaluate the feasibility of conducting follow-up activities for that condition. Follow-up activities could include obtaining medical records to confirm the diagnoses of the reported condition and conducting a study of that condition.

If, however, a condition cannot be confirmed by medical records, a study of that condition would lack scientific credibility and would not satisfy our feasibility criteria.

In addition to limited scientific credibility, additional important limitations attach to health surveys of self-reported conditions that cannot be confirmed by medical records:

1. No appropriate comparison national rates are available for these conditions. Moreover, bias in the recall of health conditions is likely. If the survey is biased in this way, then its results cannot be compared to other surveys or to national rates.
2. A selection bias will occur if those with health problems are more likely to participate in the survey than those without health problems.
3. If the survey tries to evaluate a wide range of conditions, the survey will appear to be a "fishing expedition" and will lack credibility.
4. If the survey tries to evaluate a wide range of conditions, then the survey could be overly burdensome to potential participants and the participation rate could suffer. A trade-off usually results between having a survey that is comprehensive and having a survey with a high participation rate. As the survey becomes longer and

more burdensome, it is very likely that the participation rate will decline along with its scientific credibility.

To do a credible study, it is necessary to confirm health conditions with medical records and to focus on health conditions that are likely or at least suspected of being caused by the drinking water exposure. It is also necessary to avoid biases that might occur in the selection of participants and in their willingness to participate. For these reasons, ATSDR recommends that the health survey be focused on diseases that are known or suspected to be related to solvent exposure and that can be confirmed by medical records.

Summary

Several criteria were used to determine the feasibility of future epidemiological studies at Camp Lejeune. The criteria reflect ATSDR's desire to conduct excellent and scientifically credible science. These "feasibility criteria" included:

- Minimize bias in the selection of persons into the cohort(s).
- Minimize bias in the health information obtained for each cohort member.
- Minimize bias due to risk factors other than drinking water exposures.
- Minimize bias in the assessment of exposures.
- Ensure sufficient statistical power to detect small excesses in disease rates.

In general, future epidemiological studies at the base should be capable of

1. producing scientific knowledge that is generalizable to similar situations elsewhere involving the particular exposures and diseases, and
2. answering specific questions the affected community has concerning a possible link between the drinking water exposures and diseases in that community.

ATSDR concludes that a mortality study and a cancer incidence study of cohorts of active duty Marines and naval personnel and civilian workers, including a sample from Camp Pendleton (and in the cancer incidence study—about 3,000 women from the ATSDR 1999–2002 survey), would satisfy our feasibility criteria. No bias should occur in the selection of persons into the cohort. By data linkage with federal and state vital status, mortality and cancer incidence databases, minimal loss should affect follow up and a virtually complete ascertainment of deaths and cancers. Sufficient statistical power is available to evaluate most causes of death and most cancers. Confounding due to other risk factors is a possibility, but it is unlikely that other risk factors such as smoking will be related to exposure. Variables from the DMDC personnel data can be used to adjust partially for socioeconomic risk factors. Additional evaluation of confounding can be accomplished by analyzing information on other risk factors such as smoking obtained from the Navy/USMC Health Survey.

An advantage of the cancer incidence study over the mortality study would be the ability to evaluate several female cancers (breast, ovarian, cervical, and uterine cancer) with adequate statistical power. Moreover, the cancer incidence study should have higher statistical power than the mortality study for some of the other cancers that have been associated with solvent exposure (e.g., kidney, liver, NHL, leukemia, prostate).

The results of the mortality study and the cancer incidence study can be generalized to other similar exposure situations and will address many of the questions that have been raised by the affected community.

ATSDR also concludes that, if the Navy/USMC Health Survey achieves at least a 65% participation rate, then participants—who otherwise would not be included in the data-linkage mortality and cancer incidence studies mentioned above—can be included in the cancer incidence study. The health survey would also evaluate nonfatal, noncancer diseases that can be confirmed by medical records and are known or suspected of being related to solvent exposure.

In any study conducted at the base, some bias might appear in the assessment of exposures. This is because of uncertainties in identifying locations on base where cohort members were stationed and because of possible exposures to drinking water contaminants at locations other than at the residence or work location. Such exposure misclassification bias is likely to be nondifferential (i.e., not related to disease status) and therefore likely to lead to an underestimate of the disease risk from exposure if the exposure actually causes the disease. Such a bias can also distort an exposure-response relationship. Exposure misclassification bias is a common problem in occupational and environmental epidemiological studies. The extensive water modeling that has been done at the base should, however, help to reduce the effect of exposure misclassification bias that might occur in studies at the base. Although uncertainty in the model results exists because of limited field data, the analyses of the magnitude of this uncertainty demonstrated that the uncertainty was within acceptable limits and the model results were highly reliable (ATSDR 2007).

Recommendations

In preparation for conducting a mortality study and cancer incidence study, ATSDR will work closely with the DOD on the following activities:

- Obtain personnel data for a cohort of 210, 222 Marines and naval personnel who were on active duty and stationed at Camp Lejeune anytime from June 1975 to December 1985 from the DMDC.
- Obtain personnel data for a cohort of 8,085 civilians who worked at the base anytime from December 1972 to December 1985 from the DMDC.
- Complete the computerization of the family housing records by obtaining the missing hard copy files from the base and entering these data into the family housing database.
- Prepare protocols for the mortality study, the cancer incidence study, and the health survey and submit these protocols for IRB, OMB, peer review, and agency clearance.
- Request assistance from NCI's SEER program and CDC's NPCR to gain the cooperation of state cancer registries for the cancer incidence study.
- Contact the VA, Medicare, and SSA to obtain permission to access their databases for vital status determination.
- Complete the application process for the NDI.

- Continue to work with the USMC and retired Marines to link unit codes to barracks locations on base.
- Link married active duty cohort members to the family housing database.
- Prepare materials for soliciting contractors for data management for the mortality study and cancer incidence study and conduct of the Navy/USMC Health Survey.

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.

Agency for Toxic Substances and Disease Registry. (ATSDR) 2003. Progress Report: Survey of Specific Childhood Cancers and Birth Defects Among Children Whose Mothers Were Pregnant While Living at U.S. Marine Corps Base Camp Lejeune, North Carolina, 1968–1985. Atlanta: US Department of Health and Human Services.

Agency for Toxic Substances and Disease Registry. (ATSDR) 2005a. Report of the Camp Lejeune Scientific Advisory Panel. June 24, 2005. Available at http://www.atsdr.cdc.gov/sites/lejeune/panel_report.html

Agency for Toxic Substances and Disease Registry. (ATSDR) 2005b. ATSDR Response to the Report of the Camp Lejeune Scientific Advisory Panel. 2005. Available at http://www.atsdr.cdc.gov/sites/lejeune/panel_report_response.html#1

Agency for Toxic Substances and Disease Registry. (ATSDR) 2005c. Study Protocol: Exposure to Volatile Organic Compounds in Drinking Water and Specific Birth Defects and Childhood Cancers, United States Marine Corps Base Camp Lejeune, North Carolina. May 2005.

Agency for Toxic Substances and Disease Registry. (ATSDR) 2007. Analyses of Groundwater Flow, Contaminant Fate and Transport, and Distribution of Drinking Water at Tarawa Terrace and Vicinity, U.S. Marine Corps Base Camp Lejeune, NC: Historical Reconstruction and Present-Day Conditions. Chapter A: Summary of Findings. http://www.atsdr.cdc.gov/sites/lejeune/docs/ChapterA_TarawaTerrace.pdf

Agency for Toxic Substances and Disease Registry/Division of Health Studies (ATSDR/DHS). Telephone survey of state cancer registries. No date.

Alexander DD, Mink PJ, Mandel JH, Kelsh MA. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. Occup Med Lond 2006;56:485–493.

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; 81:127–143.

Aschengrau, A; Ozonoff, D; Paulu, C; et al. Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts Arch Environ Health 1993; 48:284–292.

Aschengrau, A; Paulu, C; Ozonoff, D. Tetrachloroethylene-contaminated drinking water and the risk of breast cancer. Environ Health Perspect 1998; 106 Suppl 4:947–953.

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; 111:167–173.

Bender TJ, Beall C, Cheng H, Herrick RF, Kahn AR, Matthews R, Sathiakumar N, Schymura MJ, Stewart JH, Delzell E. Methodological issues in follow-up studies of cancer incidence among occupational groups in the United States. Ann Epidemiol 2006;16:170–179.

Bilgrad R. National Death Index PLUS: Coded causes of death. Supplement to the National Death Index User's Manual. Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention; 1997.

Blair, A; Petralia, SA; Stewart. PA. Extended mortality follow up of a cohort of dry cleaners. Ann Epidemiol 2003; 13:50–56.

Boehmer TKC, Flanders WD, McGeehin MA, Boyle C, Barrett DH. Postservice mortality in Vietnam Veterans. Arch Intern Med 2004;164:1908–1916.

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; 29:220–229.

Bosetti C, La Vecchia C, Lipworth L, McLaughlin JK. Occupational exposure to vinyl chloride and cancer risk: a review of the epidemiologic literature. European Journal of Cancer Prevention 2003;12:427–430.

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.

Bove F, Shim Y, Zeitz P. 2002. Drinking Water Contaminants and Adverse pregnancy Outcomes: a Review. Environ Health Perspect 110(S): 61–73.

Boyko EJ, Koepsell TD, Gaziano JM, Horner RD, Feussner JR. U.S. Department of Veterans Affairs medical care system as a resource to epidemiologists. Am J Epidemiol 2000;151:307–314.

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 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. 1994. Drinking water contamination and the incidence of leukemia and non-Hodgkin's lymphoma. Environ Health Perspect 102:556–61.

Collet JP, Schaubel D, Hanley J, Sharpe C, Boivin JF. Controlling confounding when studying large pharmacoepidemiologic databases: A case study of the two-stage sampling design. Epidemiology 1998; 9:309–315.

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.

Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major U.S. mortality databases. Ann Epidemiol 2002;12:462–468.

Doody MM, Chimes K. The Social Security Administration "Presumed Living" Search. Am J Public Health 2000;90:1948–1949.

Dalager NA, Kang HK. Mortality among Army Chemical Corps Vietnam veterans. Am J Ind Med 1997;31:719–726.

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

Doody MM, Chimes K. The Social Security Administration "Presumed Living" Search. Am J Public Health 2000;90:1948–1949.

Doyle, P; Roman, E; Beral, V; et al. (1997) Spontaneous abortion in dry cleaning workers potentially exposed to perchloroethylene. Occup Environ Med 1997; 54:848–853.

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;70:627–637.

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.

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;63:184–192.

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):569–577.

Goh CL, Goon A. Trichloroethylene dermatotoxicology: an update. Expert Rev Dermatol 2008; 3:173–178.

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; 8:679–680.

Gunderson EKE, Garland CF, Miller MR, Gorham ED. Career History Archival Medical and Personnel System (CHAMPS). Military Med 2005;170:172–175.

Hankey BF, Ries LA, Edwards BK. The Surveillance, Epidemiology, and End Results Program: A National Resource. Cancer Epidemiology, Biomarkers & Prevention 1999;8:1117–1121.

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, MA.

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

Institute of Medicine (IOM), Committee to Review the Health Consequences of Service during the Persian Gulf War. Health Consequences of Service During the Persian Gulf War: Recommendations for Research and Information Systems. National Academy Press, 1996.

Izquierdo JN, Schoenbach VJ. The potential and limitations of data from population-based state cancer registries. Am J Public Health 2000;90:695–698.

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 2008 (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;80:357–370.

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; 80:357–370.

Kang HK, Weatherbee L, Breslin PP, Lee Y, Shepard BM. Soft tissue sarcomas and military service in Vietnam: a case comparison group analysis of hospital patients.

J Occup Med 1986;28:1215–8.

Kang HK. Resources for Epidemiologic Research in Vietnam Era Veteran Populations within the Department of Veterans Affairs. In Epidemiology in Military and Veteran Populations: Proceedings of the Second Biennial Conference, March 7, 1990, William F. Page, (ed). Institute of Medicine. National Academy Press Washington, D.C. 1991.

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;11:504–511.

Kang H. Estimates of Cancer Prevalence in Gulf Veterans Using State Registries. Project: VA-117, Department Of Veterans Affairs 2005.

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; 677–685.

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; 527:253–263.

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; 115:1553–1556.

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; 114:213–219

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; 1076:120–128.

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; 76:473–491.

Nahleh ZA, Srikantiah R, Safa M, Jazieh AR, Muhleman A, Komrokji R. Male breast cancer in the Veterans Affairs population. Cancer 2007;109:1471–1477.

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.

National Academy of Sciences/National Research Council (NRC), National Cancer Policy Board. Enhancing Data Systems to Improve the Quality of Cancer Care. National Academy Press, 2000.

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

National Center for Veterans Analysis and Statistics, Office of Policy and Planning, DVA. 2001 National Survey of Veterans (NSV). Washington, DC: Department of Veterans Affairs, 2001. Available at: http://www1.va.gov/vetdata/docs/NSV%20Final%20Report.pdf

New Jersey Department of Health and Senior Services (NJDHSS). 2003. Case-control study of childhood cancers in Dover Township (Ocean Country), New Jersey. Trenton, New Jersey: New Jersey Department of Health and Senior Services.

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 2008 (in press).

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;107:265–271.

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; 93:248–258

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.

Ruder AM. Potential Health Effects of Occupational Chlorinated Solvent Exposure. Ann. N.Y. Acad. Sci. 2006; 1076:207–227.

Ruder, AM; Ward, EM; Brown, DP. Mortality in dry-cleaning workers: an update. Am J Ind Med 2001; 39:121–132.

Sathiakumar N, Delzell E, Abdalla O. Using the National Death Index to obtain underlying cause of death codes. J Occup Environ Med 1998;40:808–813.

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;15:445–452.

Schaubel D, Hanley J, Collet JP, Boivin JF et al. Two-stage sampling for etiologic studies. Am J Epidemiol 1997;146:450–458.

Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Pop Health Metrics 2006;4:2 available from http://www.pophealthmetrics.com/content/4/1/2

Sonnenfeld N, Hertz-Picciotto I, Kaye W.E. 2001. Tetrachloroethylene in Drinking water and Birth outcomes at the US Marine Corps Base at Camp Lejeune North Carolina. Am J Epidemiol 154(10):902–908.

Steenland K, Whelan E, Deddens J, Stayner L, Ward E. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes and Control 2003;14: 531–539.

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).

Swan SH, Shaw G, Harris JA, Neutra RR. Congenital cardiac anomalies in relation to water contamination, Santa Clara County, California, 1981–1983. Am J Epidemiol 1989;129:885–893.

US General Accounting Office (GAO). Gulf War Veterans: Incidence of Tumors

Cannot Be Reliably Determined From Available Data. GAO/NSIAD-98-89, March 3, 1998.

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; 70:1977–1985.

Wartenberg D, Reyner D, Scott CS. Trichloroethylene and Cancer: Epidemiologic Evidence. Environ Health Perspect 2000;108(suppl 2):161–176.

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

Williams-Johnson MM, Ashizawa AE, DeRosa CT. Trichloroethylene in the environment: Public health concerns. Hum Ecol Risk Assess 2001;7:737–753

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.

Yamane GK. Cancer Incidence in the U.S. Air Force: 1989–2002. Aviation, Space, and Environmental Medicine 2006;77:789–794.

Appendix A. List of Participants and Minutes of the ATSDR-Convened, Epidemiologists' Panel, Atlanta, GA, March 18, 2008.

List of Participants

1. Han Kang, Dr. PH
Director, Environmental Epidemiology Service
Department of Veteran Affairs

2. Kyle Steenland, PhD
Professor
Department of Environmental Health
Rollins School of Public Health
Emory University

3. Elizabeth Delzell, SD
University of Alabama at Birmingham - School of Public Health
Department of Epidemiology & International Health

4. Richard Clapp, ScD, MPH
Professor
Environmental Health
Boston University

5. Kenneth P. Cantor, Ph.D., M.P.H.
Senior Investigator
National Cancer Institute

6. Maria Schymura, Ph.D
Director
New York State Cancer Registry

7. Chris Rennix, CIH, Sc. D
Division Officer
Epidata Center Division
Health Promotion and Preventive Medicine Department
Navy and Marine Corps Public Health Center

ATSDR staff:

Frank J. Bove, Sc.D
Perri Ruckart, MPH
Tom Sinks, Ph.D

Minutes

General Discussion

1. Toxicity of TCE and PCE

The panel discussed whether the levels of contamination and the duration of exposure at Camp Lejeune were sufficient to cause adverse health problems in the adult population. The panel did not reach consensus on this issue. Although there have been published (e.g., CA, NJ), and unpublished (e.g., EPA's draft TCE risk assessment) cancer risk assessments indicating a 10^{-6} lifetime exposure risk at levels at or below the MCL (5 parts per billion) for TCE and PCE, there is ongoing scientific uncertainty concerning these risk estimates. Moreover, although PCE and TCE exposures at Camp Lejeune were considerably higher than their MCLs, the exposure duration was considerably less than a lifetime exposure. For example, it was pointed out by a panel member that while the average tour length for Marines is around 3 years, many had less than 3 years.

Near the end of the meeting, ATSDR staff distributed the published meta-analysis conducted by Wartenberg et al. to panel members as background material on studies that have evaluated occupational TCE and PCE exposures and adult cancers. The panel members did not discuss this paper. A question was, however, raised concerning whether the associations reported in this meta-analysis were statistically significant. ATSDR staff indicated that the meta-analysis RR estimate for TCE exposure and kidney cancer was statistically significant (RR=1.7; 95% CI: 1.1-2.7). The meta-analysis estimates for TCE exposure and liver cancer (RR=1.9; 95%CI: 1.0-3.4) and non-Hodgkin's lymphoma (RR=1.5; 95% CI: 0.9-2.3) were elevated but not statistically significant. The risk ratios for other cancers (cervical cancer, Hodgkin's disease, and multiple myeloma) and TCE exposure were also elevated but not statistically significant.

Although consensus was not reached on the toxicity of TCE and PCE, and on whether the levels and duration of exposure at the base were sufficient to cause adverse health problems among adults, the panel was in agreement that studies of mortality and cancer incidence at Camp Lejeune would be feasible and worth conducting.

2. Exposure Assessment

The panel emphasized the importance of the exposure assessment. The feasibility assessment should determine how well the DMDC personnel data on active duty marines and navy personnel can be matched to family housing records. In addition, the amount of variability in the drinking water contamination levels during the study period should be assessed to determine the feasibility of conducting internal comparisons. Issues such as the potential for active duty personnel to be living off-base instead of where their units are assigned barracks need to be addressed. For example, pay records are available that could identify those who may have lived off base or who were on assignment elsewhere (e.g., for a 6-month period), but these data are not available before 1983. Marines potentially living off-base include officers, senior enlisted, and those who were married.

The feasibility of assigning exposure to contaminated drinking water on the job for the civilian workforce, and the feasibility of assigning occupational exposures to solvents and other chemicals for active duty personnel and civilian workers, should be assessed. Finally, it should be determined whether the personnel data are sufficient to estimate accurately the duration of exposure to the contaminated drinking water.

To assess the ability to address these exposure issues, it was strongly recommended that ATSDR get all data available from the DMDC (and other possible sources within the USMC/Navy) on a subset of the active duty cohort, e.g., a sample of 500. Panel members also suggested that a similar sample of the civilian occupational cohort be taken.

Because of uncertainties in the exposure assessment, and the possibility that everyone might have been exposed to some level of drinking water contamination either at their residences or in the field, it was recommended that a sample of 50,000 Marines from Camp Pendleton be included as a comparison group to enhance the credibility of the mortality and morbidity studies.

3. Cohorts

It was recommended that ATSDR pursue the acquisition of any available data tapes of active duty Marines covering the years prior to 1975. One member of the panel indicated that information on the variables contained in such tapes is available, but that it may be difficult to find someone at DMDC who knows how to "read" these tapes. An effort should be made to determine the location of these tapes, the variables they contain, and to identify staff with the expertise and software/hardware to read these tapes.

Because the data available (so far) for active duty Marines and naval personnel start in June 1975, the panel recommended that the cohort include those who were first stationed at Camp Lejeune in June 1975 or thereafter (up to and including 1985). It was recommended also that ATSDR obtain the sample size and frequencies for this restricted cohort as soon as possible.

The panel recommended that the civilian worker cohort be evaluated separately because its exposure experience was very different from the active duty cohort. The panel noted that the sample size of this cohort may be too small to provide meaningful information on the effects of drinking water exposures. The cohort should start with those who entered civil service in 1972 or after. Exclusion of civilian workers who started at Camp Lejeune before 1974 may be necessary because date of hire may only be available from 1974 onward.

The panel strongly recommended that an extensive health survey be sent to all who receive a notification letter as well as a sample of Marines from Camp Pendleton, and that respondents be included in a study of cancer and other disease morbidity.

4. Follow-up

A. Mortality Study

The active duty cohort and the Camp Pendleton sample would be included in the mortality study. If the civilian worker cohort is of sufficient size (based on power calculations), then this cohort will be included in the mortality study but analyzed separately. Follow up would start from the date first stationed at the base. The panel noted the high cost of using the National Death Index (NDI) and therefore recommended that ATSDR consider hiring a contractor that uses a customized algorithm to determine vital status. Such an algorithm would efficiently utilize the VA BIRLS death file, the VA Medical SAS Inpatient Datasets, the Medicare Vital Status, and the SSA Death Master File. These data sources should be available free of charge to ATSDR and are updated in a more timely fashion than the NDI. These data sources provide name, date of death and state of death. Once this information is obtained, the NDI plus can be used to identify causes of death, and the death certificate can be obtained from the state's vital records. One panel member emphasized that if the full name is not available from DMDC data, it could be reconstructed through SSA or IRS searches.

B. Cancer Incidence Study

1. Cancers diagnosed from 1997 onward ("Data linkage approach")

The active duty cohort and the Camp Pendleton sample would be included in the cancer incidence study. The civilian employee cohort will be included, and analyzed separately, in the study if statistical power is sufficient. The name, SSN and date of birth would be sent to all 50 state cancer registries to match with their data from 1997 (when data from all states are available) to the end of follow-up. The registries would provide tumor characteristics and date of diagnosis.

2. Cancers diagnosed at any time after first stationed at the base ("Health survey and data linkage approach")

The panel discussed matching the personnel data with cancer data prior to 1997 (e.g., from states that had registries in operation prior to 1997 or data from other sources such as DOD's ACTUR, the VA's VACCR, and the Navy's CHAMPS). The panel also discussed using the health survey to identify cancers diagnosed prior to 1997.

One panel member suggested that all cancers identified before 1997 could be used, and person-time would start accruing from the time the person first was stationed at the base. Such a cohort might be limited to those who responded to the survey, especially if it is likely that cancer data (e.g., from state registries) will not cover a large part of the at-risk period,(i.e., from date first stationed at the base until 1996). The feasibility of this approach depends on the health survey having a good response rate, on the order of 60%–70%. It would be necessary to include next-of-kin of decedents in the survey.

If the health survey cannot achieve a satisfactory participation rate, then a study based solely on data linkages may be appropriate. Panel members pointed out that the active duty cohort is relatively young and that many cancer registries have data prior to 1990 so that underascertainment of cancers occurring prior to 1997 may not be a serious problem. The data linkage approach would include all the cancers identified by ACTUR, VACCR, and CHAMPS as well as data from each state cancer registry from the start of its operation until the end of the study. The active duty cohort and the Camp Pendleton sample would be included in this study as would the civilian worker cohort if it is of sufficient size. Follow-up would begin from the date first stationed at the base.

C. Health Survey

The panel strongly recommended that the health survey include questions on a wide range of nonfatal diseases that can be confirmed by medical records, including cancers and other diseases known or suspected of being associated with solvent exposures. The survey should also include questions on risk factors such as smoking and occupational exposures, and questions about residences and activities on base. On the other hand, the survey should not be so burdensome that the participation rate suffers. ATSDR should emphasize to the Navy/USMC that the survey can provide information on important, non-fatal diseases besides cancers as well as information on potential confounders and on residences and activities at the base.

The panel strongly recommended intensive procedures to convert nonresponders, including repeat mailings and phone contacts. It was recommended that ATSDR present a tiered-approach to nonrespondent conversion to the Navy: the expected increase in participation rate from several repeated mailing and its cost; and the expected increase in participation rate from following up the mailings with phone contacts and its cost. One panel member suggested a goal for participation rate of at least 75%. Others suggested rates in the 60% to 70% range.

Although the panel recommended that a pilot study evaluating the most efficient methods of nonrespondent conversion be conducted on a sample of 1000–1500 participants, the panel realized that this might not be possible given the time constraints imposed by the federal law mandating the survey. The panel suggested that ATSDR ask Congress for permission to conduct a pilot study before the large-scale mailing begins.

The panel strongly recommended that ATSDR determine how the Navy/USMC is obtaining current addresses to make sure that appropriate procedures are being used. The panel noted that the biggest obstacle to participation is often failure to locate and contact the study subject.

One suggestion was for the notification effort to mention that the survey is coming, confirm the address, obtain consent, and then the survey would be mailed to the participant.

The panel strongly recommended that the health survey be sent to the next-of-kin if the study subject has died. The next of kin could be identified from the death certificate. If the decedent was on active duty after September 1983, then the DEERS database could be used to identify next of kin. (DEERS started in 9/83).

Finally the panel suggested that a monetary incentive might be necessary to increase the participation rate. One suggestion was an incentive of $50.

5. Health Outcomes

There was some discussion concerning the health outcomes that would be expected from exposures to the contaminated drinking water during one tour of duty (3-4 years for enlisted personnel, 4-6 years for officers), although many (approx 20%, see appendix of the draft feasibility assessment) serve more than one tour.

The meta-analysis of TCE conducted by Wartenberg et al. was handed out. So far, there has been no meta-analysis of PCE. From the occupational literature, the meta-analysis identified several cancers associated with TCE exposure: kidney cancer (RR=1.7), liver cancer (RR=1.9), and non-Hodgkin's lymphoma (RR=1.5), with possible elevations also for cervical cancer, Hodgkin's disease, and multiple myeloma. A drinking water study conducted in NJ also found an association between TCE and non-Hodgkin's lymphoma and chronic lymphocytic leukemia. A 2003 Danish cohort study also found an association between occupational exposure to TCE and esophageal cancer. Finally, recent occupational studies suggest possible associations with end stage renal disease and Parkinsonism.

Drinking water studies of PCE in Cape Cod and NJ have found associations with non-Hodgkin's lymphoma, leukemia, and breast, lung, bladder, and colon/rectal cancers. Occupational studies of PCE exposure have suggested associations with the following cancers: lung, esophageal, bladder, cervical, and non-Hodgkin's lymphoma.

6. Ongoing Expert Panel

The panel recommended an ongoing expert panel be convened as needed to discuss decision points and other methodological issues that arise.

Discussion of the Questions

All causes Mortality Study

1. We do not have the raw data from the DMDC, but a rough estimate is that about 25% to 35% of the active duty Marines and navy personnel at Camp Lejeune may have been unexposed to the drinking water contamination. Should there be a second unexposed comparison group, (e.g., active duty personnel from another Marine base such as Camp Pendleton)?

   Discussion:
   How much variation is expected in the exposure levels? ATSDR should use a second unexposed comparison group such as Camp Pendleton.

1. There are 8,085 members of the civilian occupation cohort. Should we include this cohort in the study given that some may have had occupational exposures to solvents and other chemicals? Should the cohort be included in the study but analyzed separately?

   Discussion:
   After ATSDR conducts an exposure assessment of this cohort, it can answer this question. It is likely, however, that this cohort will need to be analyzed separately. A statistical power analysis should be done to determine whether it is worthwhile studying this cohort at all because of its small size. The cohort should start with those who entered civil service in 1972 or after. Still, information on date of hire may not be available until 1974.

1. Is it necessary to use the SSA data to determine vital status or can just the NDI be used?

   Discussion:
   ATSDR should use other databases (such as SSA, BIRLS) to find out the vital status of the cohort members and then just send the decedents to NDI. However, SSA will return a fairly large portion of unknown or unmatched data. ATSDR should use a contractor with a customized algorithm to determine vital status.

1. How should a latency period be handled: lagging exposure, or beginning follow-up after a minimum time period, (or some other method)?

   Discussion:
   Latency should be handled in the analyses.

1. Should comparisons be made to U.S. mortality rates or should only internal comparisons (and possibly comparisons with another Marine base) be conducted? (Should we be concerned about a healthy veteran effect?)

Discussion:
ATSDR should use an external control group for scientific credibility (given the uncertainty that there were unexposed at the base) and political reasons, such as 50,000 former Marines from Camp Pendleton. If the civilian cohort at Lejeune is studied, then civilian workers from Camp Pendleton are also needed.

1. For those active duty members who were stationed at the base prior to June 1975, we will not have information from computerized personnel records indicating when they were first stationed at the base and how long they were stationed at the base prior to June 1975. How should we handle this problem when characterizing drinking water exposures?

   Discussion:
   ATSDR should define the active duty cohort as those who entered Camp Lejeune in 1975 or later. ATSDR needs to get from DMDC the number of active duty personnel who started in 1975 or later.

<u>Cancer Incidence Study</u>

1. Which of the proposed approaches do you think are feasible and warranted? What are the problems you see with each of the proposed approaches? Do you have other suggested approaches?

   Discussion: not specifically addressed, but methods were discussed.

2. Should we include cancer deaths in the cancer incidence study?

   Discussion: Yes

3. Should we include self-reported cancer cases that are not confirmed by medical records or cancer registrations?

   Discussion: Include confirmed cases only.

4. What questionnaire items should be included in the Navy/USMC health survey?

   Discussion:

   Health outcomes that are known or suspected to be related to the exposure, based on occupational and drinking water studies, including cancers, kidney diseases, liver diseases, neurological diseases, and autoimmune diseases.

Items should also include residential history, occupational history, questions about other risk factors that could act as confounders, and questions about activities on the base.

5. What response rate would be credible and what procedures would you suggest to meet that response rate?

   Discussion:
   60–75%. ATSDR needs a systematic process for follow up of nonrespondents and a protocol for converting nonrespondents. Offer an incentive to complete the survey, but give an extra incentive to initial nonrespondents.

6. How should a latency period be handled: lagging exposure, or beginning follow-up after a minimum time period, (or some other method)?

   Discussion: deal with this issue in the analyses.

7. Is it safe to assume that there are comprehensive data on cancers for those on active duty and for civilian employees at DOD facilities up to the time they retire? If so, how far back in time do these data go?

   Discussion: not discussed.

Appendix B. Cancer Mortality and Cancer Incidence: Expected And Detectable SMRS and SIRS With 10-Year Lag

Cancer	10 year lag Mortality Expected #	Minimum Detectable SMR*	10 year lag Incidence Expected #	Minimum Detectable SIR*
Esophageal	39	1.54	50	1.47
Colon/rectal	100	1.32	340	1.17
Liver	51	1.47	70	1.39
Kidney	33	1.60	165	1.24
Pancreas	53	1.45	65	1.40
Lung	227	1.20	320	1.17
Bladder	11	2.15	133	1.27
Brain	73	1.37	135	1.27
NHL♦	55	1.44	282	1.18
Leukemia	55	1.44	128	1.28
Myeloma	14	1.93	40	1.54
Prostate	8	2.37	305	1.18
Cervix	3	3.51	15[**] / 21[***]	1.95[**]/1.78[***]
Breast	12	2.06	81[**]/120[***]	1.36[**]/1.28[***]
Uterus	<1	-	10[**] / 15[***]	2.13[**]/1.95[***]
Ovary	2	4.64	8[**] / 10[***]	2.37[**]/2.13[***]

* The minimum detectable SMR or SIR is the lowest SMR or SIR that can be detected at 90% statistical power (i.e., a "Type 2 error" of .10), and a "Type 1 error" (or α error, 2-sided) of .10 which is equivalent to using a 90% confidence interval or p-value $_{\text{(2-tailed)}}$ of .10 to determine statistical significance. An SMR (Standardized Mortality Ratio) or an SIR (Standardized Incidence Ratio) indicates how many times higher the rate of disease is in an exposed group compared to the national rate.

♦ Non-Hodgkin's lymphoma

** active duty women only

*** active duty women plus women from the ATSDR 1999-2002 survey

Expected numbers are based on age-specific U.S. mortality (1999-2004) and U.S. cancer incidence (1999-2002) rates and assumes complete ascertainment. The cohort consists of approximately 170,000 Navy and Marines who were stationed at Camp Lejeune anytime between June 1975 and December 1985, and who began active duty service in June 1975 or later. If a 10 year latency period is assumed, then the cohort would contribute almost 3 million person-years of follow-up starting from 10 years after the start of assignment at Camp Lejeune to 2007.

To estimate the number of cancers of the breast, cervix, uterus, and ovary, the amount of person-years that would be contributed by approximately 6,000 female Marines and navy personnel was estimated. Assuming a 10 year latency period, it was estimated that women in this cohort would have contributed approximately 106,000 person-years. If approximately 2,900 women from the ATSDR 1999-2002 survey who first resided at the base between 1975 and 1985 are added to the cohort for the analysis of cancer incidence, then the total person years would be approximately 157,000.

Appendix C. State of Residence for USMC Retirees and Cancer Registry Data by State.

State	% retirees	Cancer registry data available	% complete	State	% retirees	Cancer registry data available	% complete
CA	15.38	1988	100.0	NJ	1.01	1979	99.0
NC	10.24	1990	93.0	WI	1.01	1978	100.0
VA	8.52	1990	88.6	KY	.95	1991	99.4
FL	7.79	1981	99.7	HI	.89	1973	100.0
TX	6.52	1992	92.9	AR	.87	1996	85.6
GA	3.52	1995	79.5	MS	.86	.	.
AZ	3.17	1995	86.0	MN	.73	1988	99.9
PA	2.93	1985	100.0	NM	.73	1973	94.9
SC	2.76	1996	97.3	KS	.72	.	.
TN	2.26	1989	.	WV	.63	1993	99.5
MD	2.16	1982	.	IA	.56	1973	100.0
OH	2.15	1996	94.1	ID	.52	1970	97.8
WA	2.06	1992	100.0	CT	.46	1935	100.0
NY	1.97	1976	100.0	ME	.45	1983	97.4
MO	1.96	1985	100.0	UT	.43	1966	96.0
IL	1.76	1986	100.0	NH	.38	1987	95.8
AL	1.58	1996	79.3	MT	.37	1979	97.1
MI	1.52	1985	100.0	NE	.33	1987	99.7
NV	1.43	1995	91.2	RI	.21	1986	100.0
IN	1.34	1987	91.2	DE	.21	1972	99.2
CO	1.32	1988	100.0	SD	.16	.	.
OR	1.22	1996	99.2	DC	.14	1987	100.0
LA	1.18	1988	95.5	AK	.14	1996	100.0
MA	1.11	1982	98.7	WY	.14	1962	94.8
OK	1.04	.	.	VT	.13	.	.
				ND	.07	1997	97.3

Source: USMC; NAS, 2000; ATSDR/DHS, no date

Appendix D. Home State of Residence for Active Duty Cohort and Cancer Registry Data by State

Home State	% retirees	Cancer registry data available	% complete	Home State	% retirees	Cancer registry data available	% complete
NY	10.3	1976	100.0	MS	1.0	.	.
PA	7.2	1985	100.0	WA	0.9	1992	100.0
OH	7.0	1996	94.1	AR	0.8	1996	85.6
FL	5.0	1981	99.7	CO	0.8	1988	100.0
IL	4.7	1986	100.0	OK	0.8	.	.
CA	4.4	1988	100.0	AZ	0.7	1995	86.0
MI	4.2	1985	100.0	ME	0.7	1983	97.4
NC	4.1	1990	93.0	KS	0.7	.	.
TX	4.1	1992	92.9	NH	0.6	1987	95.8
NJ	3.9	1979	99.0	OR	0.6	1996	99.2
VA	3.2	1990	88.6	DC	0.5	1987	100.0
MA	2.9	1982	98.7	NE	0.5	1987	99.7
IN	2.9	1987	91.2	RI	0.5	1986	100.0
MD	2.8	1982	.	NM	0.5	1973	94.9
GA	2.8	1995	79.5	DE	0.4	1972	99.2
MO	2.1	1985	100.0	ID	0.2	1970	97.8
TN	2.1	1989	.	VT	0.2	.	.
WI	2.1	1978	100.0	SD	0.2	.	.
AL	2.1	1996	79.3	MT	0.2	1979	97.1
SC	1.9	1996	97.3	ND	0.2	1997	97.3
KY	1.8	1991	99.4	NV	0.2	1995	91.2
CT	1.6	1935	100.0	UT	0.2	1966	96.0
LA	1.5	1988	95.5	HI	0.1	1973	100.0
MN	1.4	1988	99.9	WY	0.1	1962	94.8
WV	1.2	1993	99.5	AK	0.1	1996	100.0
IA	1.0	1973	100.0				

Source: DMDC; NAS, 2000; ATSDR/DHS, no date

Appendix E. Demographics of DMDC-Identified Cohort

AGE (in 2007)	**Marine**s	Navy	Total
35-44	21.1%	14.0%	20.7%
45-54	68.0%	56.5%	67.4%
55-64	8.7%	22.2%	9.4%
65-74	2.0%	6.0%	2.2%
≥ 75	0.3%	1.3%	0.3%

Marines = 198,805
Navy = 11,417

Sex

	Marines	Navy	Total
Female	3.6%	9.4%	8,214 (3.9%)
Male	96.4%	90.6%	

Pay Grade

	Marines	Navy
Enlisted	95.2%	84.4%
Warrant	0.3%	0.2%
Commissioned	4.5%	15.4%

Years of active duty service

	Marines	Navy
1 – 11 months	21.3%	10.2%
12 – 23 months	16.2%	11.1%
24 – 35 months	20.3%	15.5%
36 – 47 months	21.7%	22.6%
48 – 59 months	5.7%	8.8%
60 – 71 months	2.4%	4.5%
72 – 83 months	2.1%	3.1%
≥ 84 months	10.4%	24.1%

Race/ethnicity

"white"	72.9%
African American	24.5%
Hispanic	3.9%

Appendix F. Demographics of DMDC-Identified Civilian Occupational Cohort

Total = 8,085

54.4% male
45.6% female
76.5% “white”
21.7% African American

AGE (in 2007)

35-44	1.0%
45-54	19.3%
55-64	30.3%
65-74	18.9%
≥ 75	30.5%

Years of service

< 1 year	32.0%
1 year	7.0%
2 years	3.3%
3 years	3.9%
4 years	3.5%
5 years	4.0%
6 years	3.6%
7 years	3.0%
8 years	2.5%
9 years	2.2%
≥10 years	35.0%

Appendix G. Description of Cohorts for Future Studies

Cohort*	Description	Data Elements	Study

DMDC-identified active duty cohort	• 210,222 Marines and navy personnel who were stationed at Camp Lejeune any time during June 1975 to December 1985
	   o 8,214 women
	   o 70% single
	• Cohort would include those who began active duty service in June 1975 or later (approximately 160,000-170,000) because no data are available on duty station prior to June 1975
	• Approximately 3 million person-years if follow-up is started after a 10-year lag from the date first stationed at Camp Lejeune to 2007
		• Partial last name (1975-1976)
		• Full name (starting in 1977)
		• SSN
		• Date of birth
		• Sex
		• Race/ethnicity
		• Years of active duty
		• Dates of service
		• Unit code
		• Occupational Specialty (MOS)
		• Marital status
		• Number of dependents
		• Education level attained
		• Pay grade
		• Home of record
			• Mortality
			• Cancer incidence

DMDC-identified civilian occupational cohort	• 8,085 civilians who worked at Camp Lejeune any time during December 1972 to December 1985 o 3,687 women • Cohort would include those who began employment at Camp Lejeune in June 1974 or later (approximately 6,000) because data on employment before June 1974 is not available	• Full name (starting Dec. 1981) • SSN • Date of birth • Sex • Race/ethnicity • Years of service • Dates of service • Marital status • Number of dependents • Education level attained • Pay grade • Home of record • Occupational code	• Mortality • Cancer incidence

		• Location of occupation	
ATSDR 1999-2002 Survey	• 12,598 respondents and their spouses who participated in the telephone survey conducted from September 1999 to January 2002 as part of the current case-control study of specific childhood cancers and birth defects. • Many survey participants (about 4,100 marines and navy personnel who left the base prior to June 1975 and over 12,000 spouses of military personnel) would not be included in the DMDC-identified cohorts • Adding women participants who first resided at the base during 1975-1985 would add about 2,900 to the cancer incidence study	• Full names • Address at the time of the survey • Dates of birth of the parents • Dates the parents lived on base • Address of on-base family housing unit • Most respondents provided their SSNs	• Cancer incidence

* ATSDR concluded that the number of students that could be identified from high school transcripts and the alumni association was insufficient for a future study because of damaged cartridges containing the transcripts and incomplete data available from the alumni association. DMDC's Defense Enrollment Eligibility Reporting System (DEERS) has information on family members of active duty and retirees beginning in September 1983 which is near the end of the drinking water contamination period. No other DMDC database appeared to be useful for identifying children or other family members.

Appendix H. Description of Relevant Drinking Water Systems

Drinking water system	Description	Housing area served*	Data sources
Tarawa Terrace	• Contaminated with PCE from Nov. 1957-February 1987 at levels > current MCL of 5 ppb • Heavily contaminated wells shut down in February 1985 • All wells shut down by March 1987	• Tarawa Terrace • Knox Trailer Park - primarily served by Tarawa Terrace	• Family housing records • Navy/USMC Health Survey • Occupation code and location of occupation from DMDC data – depends on ability to link water source to the workplaces of civilians who worked at the base
Holcomb Blvd	• Constructed in June 1972 • Not contaminated with solvents	• Watkins Village (constructed in 1977)**, Berkeley Manor, Midway Park, Paradise Point - After June 1972	• Family housing records • Navy/USMC Health Survey • Occupation code and location of occupation from DMDC data – depends on ability to link water source to the workplaces of civilians who worked at the base
Hadnot Point	• Still being modeled. • TCE was found at 1400 ppb, t-DCE > 300 ppb, and benzene and pesticides were found in the water.	• Berkeley Manor, Midway Park, Paradise Point** - Prior to June 1972 • Watkins Village, Berkeley Manor, Midway Park, Paradise Point - Jan. 27-Feb. 7, 1985 because a pump needed repairs • Hospital Point • Most of the barracks/bachelor's quarters • Occasionally re-supplied Holcomb Blvd during dry summer months	• Family housing records • Navy/USMC Health Survey • Unit code will be linked to barrack areas on base using information from retired Marines and the USMC • Occupation code and location of occupation from DMDC data – depends on ability to link water source to the workplaces of civilians who worked at the base

*Note: Courthouse Bay, New River, Camp Geiger, Camp Johnson, Rifle Range - served by drinking water systems not contaminated with solvents

** Some homes on Virginia Street in Watkins Village area were constructed in 1961 and would have received Hadnot Pt water until June 1972.

Appendix I. Information on Base Housing and Workplace Locations

Source of information	Description	Use	Linkage with cohort
Family housing records	• Name of occupant assigned to housing, street address, dates of residency, and rank • ~ 90,000 records • 74,980 records were computerized by ATSDR • ~ 15,000 records missing from ATSDR's storage area • Consider recovering records by looking through hard copies on base • Approximately 4,815 base family housing units	• Useful for drinking water exposure assessment for Marine/Navy personnel assigned to base family housing and their families • Names and dates of occupancy of those assigned to family housing can be linked with DMDC data • **Limitation**: unique match between housing records and DMDC data may not be possible for many of the cohort members assigned to family housing without additional information	• DMDC-identified active duty • ATSDR 1999-2002 Survey participants

Unit code (active duty personnel)
Occupation code and Location of occupation (civilian)
	• Available from the DMDC data
	• About 70% of active duty Marines and navy personnel were single
	• Most single active duty Marines and navy personnel resided in barracks
	• Issues to resolve:
	  o Date women were integrated with their units
	  o Date the 8th regiment moved to Geiger from mainside
		• The unit code and description will be used to determine barrack locations based on information from retired Marines and USMC. Data on the drinking water system serving the barrack area will be used to assign exposures.
		• Occupation code and location of occupation may be valuable for linking water source to the workplaces of civilians who worked at the base
			• DMDC-identified active duty
			• DMDC-identified civilian occupational

Navy/USMC Survey	• Survey will include a request for information on residential history on base and on occupation location on base	• Information will be used, along with other data, to identify location of residence or workplace on base.	• All cohorts • ATSDR survey participants • All who register

	• Survey will be mailed in early 2009.		with USMC or ATSDR

Appendix J. Health Outcome Information

Source of information	Description	Study
NDI and NDI-Plus	• Useful for determining deaths occurring from 1979 onward among cohort members who resided in U.S., Puerto Rico, or the Virgin Islands • NDI provides state of death, date of death, and death certificate number • NDI-Plus provides ICD-9 codes for the underlying and multiple ("contributing") causes of death	• Mortality • Cancer incidence o Cancer deaths will be included

Social Security Administration (SSA) Death Master File	• Useful for determining vital status of the cohort members; provides one of the following vital status determinations for each cohort member:
	  o Deceased (residence state and date of death)
	  o Presumed Living (based on all SSA databases)
	  o Status Unknown
	  o Failed SSN/invalid SSN
	• Can identify deaths occurring in foreign countries
		• Mortality

Veterans Affairs Beneficiary Identification and Record Locator Subsystem (BIRLS) Death File (created in 1970) Medicare Vital Status file for Medicare-enrolled veterans	• BIRLS contains records of all VA beneficiaries including veterans whose survivors apply for a death benefit o Provides date and state of death • These databases can be used in conjunction with the SSA Death Master File in an algorithm to determine vital status	• Mortality
Navy/USMC Survey	• Mailing requesting information about cancers and non-fatal, non-cancer diseases diagnosed by health providers (type of cancer, date of diagnosis, and state and hospital of diagnosis) • Facilitates acquisition of cancer registry data or medical record confirmation • Requests medical records or access to medical records	• Cancer incidence • Non-fatal, non-cancer diseases

State cancer registries	• Exist in every state but vary in quality and coverage periods • Some states have data beginning in 1979 or earlier; at least 10 states did not have cancer registries in 1990 • Vary in willingness to share data with researchers • Some registries have problems with duplicate reports and reporting delays	• Cancer incidence
CHAMPS (NHRC's Career History Archival Medical and Personnel System)	• Captures disease requiring hospitalization among active duty personnel • Data on active duty marines begins in 1980	• Cancer incidence
VACCR (Veterans Affairs Central Cancer Registry)	• Established in 1995 • Aggregates the data collected by the tumor registries of the approximately 120 VA medical centers diagnosing and/or treating patients with cancer • Only 10-20% of veterans receive care from the VA	• Cancer incidence
ACTUR (DOD Automated Central Tumor Registry)	• Established in mid-1986 • DOD's main cancer data collection and reporting system • Covers hospitalizations of active duty personnel, retirees, and family members at military treatment facilities • Essentially a passive surveillance system • Completeness of reporting by the DOD treatment facilities is unknown • Most veterans do not receive care from DOD medical facilities after discharge	• Cancer incidence