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COVER SHEET FAX

To: Kelly Dreyer
USMC HQ, Arlington VA

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Subject: REVIEW OF ATSDR "CAMP LEJEUNE CHILDHOOD LEUKEMIA STUDY PROPOSAL"

Date: 08 August 1997

Pages: 12 including this cover sheet.

COMMENTS:

Kelly,

As I discussed with you, I asked Dr. Jeffrey Hyman, an epidemiologist at Navy Environmental Health Center, to review the subject ATSDR proposal as well as the "Woburn study" which is refered to in the proposal. He provided a comprehensive review of the study, which I am forwarding you as a fax. I have previously forwarded the review to Wade Jensen, NAVFAC HQ, and to Dr. Kathleen Buchi, ATSDR/DOD Program Lead Agent. We are in agreement that, per Dr. Hyman's recommendation, we first conduct a pilot study to determine if there is any increase in childhood leukemia in dependents of Marine Corps personnel. This should be used as the basis to determine whether a larger study is needed or not.

Very respectfully,
Andrea

From the desk of...

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Review of "Camp LeJeune - Childhood Leukemia Study Proposal"

Proposed investigators - ATSDR

Reviewer -Jeffrey Hyman, Ph.D.

Contents

I. Background

Between 1969 and 1989 there were 21 cases of childhood leukemia (CL) in Woburn, Mass. This represented an excess of about 14 cases. 9 (43%) of the cases occurred in children aged 4 or younger. A number of studies have been conducted on this population, most recently (and perhaps most comprehensively) the Woburn Childhood Leukemia Follow-Up Study (WCLFS) by the Massachusetts Department of Public Health.

The WCLFS found increases in leukemia risk among those children whose mothers drank water during their pregnancies that came from Wells G and H. In fact the early excess of CL was concentrated in one census tract in East Woburn that was served by Wells G and H. These wells were in operation from 1964 to 1977, provided 24% of the cities water, and drew water from the contaminated Aberjona aquifer. Up to two thirds of the city received at least some contaminated water.

At various times the wells were contaminated with trichloroethylene (267 ppb), tetrachororethylene (21 ppb), chloroform, methyl chloroform, trichlorotriflouroethane, 1,2-dichloroethylene, 1,1,1-trichloroethane, arsenic, lead, chlordane, and vinyl chloride.

Estimating exposure to the contaminated water was a great challenge, which was met in the WCLFS by querying participants on water usage and by developing a complex "Murphy" water distribution model using water billing recoreds, water distribution pipe size and network network design. The model was carefully validated using fluoride measurements.

The WCLFS found that the greatest risk of CL was associated with exposure to this water during pregnancy, with an adjusted odds ratio (OR) =4.9 for the most exposed (7 cases), and OR=1.0 for the least exposed. By using the statistical technique of composite covariates these odds ratios were increased to 14.3 and 3.5 respectively. However since such a small number (10) of cases received any exposure, none of the results were statistically significant..

CL risk factors were found in the Woburn population that were not related to contaminated water. These included: father working in a high risk industry (OR=2.4), maternal alcholol use during pregnancy (OR=1.5), breast feeding (OR=0.6 with a CI

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small number of cases), paternal grandfather with a cancer diagnosis (OR=2.0), and maternal exposure to x-rays (OR=10.4 with only 6 cases and 2 controls) .

II. Weaknesses of the Woburn Studies

Small # of cases

• The greatest problem was the small number of cases, which prevented the researchers from statistically demonstrating that the observed associations between contaminated water and CL were not due to chance. It also made it difficult to evaluate confounding variables.

dynamic hydro-geo makes contaminant blend impossible

• Changes in water contamination over time. ATSDRs own assessment of Wells G and H found that the hydrogeologic characteristics in the areas of the wells are "dynamic". The WCLFS report stated that: "Given this fact it would be difficult to predict historically which areas of contamination fed the wells over which time periods. It would therefore be impossible to determine the exact blend of contaminants at any given time." This further clouded the association between water contaminants and CL.

• Multiple contamination The many contaminants found in Wells G and H, including various heavy metals, makes it impossible to isolate the effects of individual chemical contaminants on any CL increase. The WCLFS report stated that: "Because testing of the wells was very limited, a clear picture of the extent and nature of contamination, as well as the history of contamination is not known."

metals influence

• Inability to investigate the possible role of infectious agents.

other influences

III. Woburn Conclusions.

The WCLFS stated that "These odds ratios, although not statistically significant suggest that the relative risk of developing childhood leukemia was greater for those children who were exposed to water from Wells G and H from their mother's consumption of water particularly during pregnancy." "....Odds ratios suggest that the relative risk of developing childhood leukemia among children who consumed water from Wells G and H from their birth through childhood was virtually identical for cases and controls."

The WCLF study was unable to relate the excess risk to any individual contaminant due to the many organic and inorganic substances in the water. They stated that "Based on the currently understood data regarding TCE exposure, a link between TCE exposure and

Wells G and H and human health effects seems weak. Due to the lack or data regarding the effects of TCE on a developing fetus, however, the plausibility cannot be dismissed." and "It is interesting to note that human studies of TCE exposure in populations have not demonstrated an increased risk of leukemia."

In fact research is still ongoing to determine the possible role of exposure to heavy metals in the Woburn CL cluster.

IV. Scientific Value Of Proposed Camp LeJeune Study.

The inability of the Woburn studies to conclusively demonstrate a possible association between volatile organic chemicals (VOC) such as TCE and childhood leukemia is very frustrating, and it is easy to understand the desire of the ATSDR researchers to conduct a similar study on another (Camp Lejeune) population that was exposed to VOCs.

ATSDR reports that 6,362 infants were born to families living in the Tarawa Terrace housing areas of Camp LeJeune during 1958 to 1985. A further 32 births occurred to families living in the more contaminated area of Hospital Point. There is also a control population of 5898 families at other housing areas. (At other points in their proposal they state that the study interval is 1968 to 1985) Based on population and Surveillance, Epidemiology, and End Results (SEER) Program incidence rates, there were expected to be 7.2 cases among 10,000 families that they hope to contact.

Unfortunately, every problem that existed in Woburn and limited the conclusions of the WCLFS exist in at least as severe of a form in the Camp LeJeune population.

• Study Power. The proposed study will have severe problems with sample size and statistical significance. The expected 7.2 cases of CL at Camp LeJeune is virtually identical to the expected number in Woburn. Even assuming that they could actually locate and enroll 83% of the 12,000 families (which seems virtually impossible, see section V), this study would have (at best) no more power then the Woburn studies. The ASTDR proposal states that "...even findings that are not statisticaly significant can provide information of the most likely range of values for the association between exposure and outcome." It

would be very difficult to justify an expenditure of 1.8 million dollars on the basis of this study goal.

In addition, there are other factors which could further decrease study power. The contamination pattern detected at Tarawa Terrace in Camp LeJeune differs from that found in Woburn, with a TCE level of 8 ppb versus 267 ppb in Woburn. The primary contaminant at Camp Lejeune is tetrachororethylene (215 ppb) versus 21 ppb in Woburn. ATSDR reports that a study in Barnstable County, Mass. found an overall odds ratio for CL of 2.0 associated with water that contained 7750 ppb of tetrachlororethylene. If the expected association between VOCs and CL is based on TCE contamination, the very low levels at Camp LeJeune could greatly decrease the actual number of excess CL in this population.

	MCB	Woburn
TCE	8	267
PCE	215	21

The incidence of CL is about twice as high in white children as in black. If the racial diversity of the Camp LeJeune population was substantially greater then existed in Woburn, the actual number of expected cases could be lower then 7.2.

- Exposure determination. The ASTDR proposal suggests that water usage estimates will be based on interview data. If this is their plan, it will provide much weaker exposure data then was used in Woburn.
- Unknown number of cases. We have no information of the number of CL cases in this population. This makes it impossible to evaluate the completeness of the case ascertainment. Given the very small expected number of cases and the resulting instability of the risk estimates, this will always cast doubt on the study results.
- Unknown stability of water contaminants. The proposal states that water contamination was detected as late as 1985 and was recently quantified. It does not provide any information to indicate that ATSDR has investigated possible changes in the amount and composition of the contamination during the study period. They also don't mention if they know when the contamination started.
- Control populations. The ATSDR proposal suggests using national CL rates as a control population to increase study sensitivity. However the Camp LeJeune population is subject to continual population mixing. This mixing has been implicated as a CL risk factor and has been associated with leukemia clusters. The mixing is thought to facilitate viral transmission. This theory holds that viruses function as promoters, which act on previously

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transformed cells. While it is intriguing to consider the possibility of prenatal exposure to environmental contaminants acting as transforming agents, this possibility will only complicate the interpretation of any Camp LeJeune results. Unless prior studies have demonstrated that there is no increased risk of CL at large military bases, then only military populations be used as control groups.

In summary, it is very difficult to see how, even if successfully completed, this study could contribute anything to our understanding of the relationship between VOCs and childhood leukemia.

V. Feasibility of the Camp LeJeune Proposal.

A. Case Ascertainment Woburn has a very stable population, which makes it easier to locate people. In addition, the names and addresses of all 21 cases were known to the WCLFS researchers ahead of time. Under these very favorable circumstances they were able to obtain the participation of 19 of 21 cases (90 %) and 21 of 38 (55%) of the original controls.

In the proposed Camp LeJeune study, ATSDR expects to locate and obtain participation from 83% of a very mobile military population when they do not even know the number of cases, their names, the social security numbers or current addresses of anyone in the population. They have not explained how privacy act considerations may affect their ability to obtain the information of the study population from military sources..

mobile population to find and to track.

Further complicating the problem are the passage of time (12 to 29 years), changes in the last name of up to 51% of the children (as the girls get married) and a substantial percentage of the mothers (due to divorce or remarriage). The frequent moves of military personnel also suggests that part of the "exposed" population was not living at Camp LeJeune for their entire pregnancies, which further reduces statistical power and complicates exposure determination.

The ATSDR proposal states that "tracing will present quite a challenge,...". Unless the ATSDR researchers are able to demonstrate that they have been able to achieve an 80-85% response rate from a similar population (in terms of size, time, rare outcome, mobility,

lack of social security number and other identifiers) in the past, their proposal should be rejected as totally unworkable, and a probable waste of almost 2 million dollars.

B. Cost It is difficult to evaluate the cost of the ATSDR proposal based on the limited information provided. We do not know what part of the work will be contracted out and whether competitive bids have been obtained. We do not know the number of ATSDR employees who will work on the project, their labor hours, salaries, overhead rates, or what equipment and administrative costs are being charged to this study. There is no explanation of why data entry and management will cost $250,000. There is also no explanation of what will be done with the excess funds if the expected 83% of the population does not participate.

Cost estimate are not spelled out and there is nothing else to compare it to.

It is noted in passing that interviews (by telephone?) are projected to cost $150 each, record tracing will cost $154 each for 5000 records (it's difficult to see why 5000 records will be traced for 6-20 cases and up to 80 controls), and verification of medical diagnoses will cost $150 each for 100 records.

Most importantly, we do not have any other proposals to compare these cost estimates to.

VI. Proposed Method of Evaluating and Funding Studies.

The ATSDR proposal illustrates many problems generally associated with sole source, non-competitive contracts. It is extremely expensive, poorly thought out, has little chance of being successfully completed and providing useful information, and it lacks the detailed information that any competent funding agency would demand before considering it.

If the Navy is to be responsible for evaluating and funding environmental Epidemiology studies on military personnel, then it is our responsibility to develop a mechanism to do this in a professional manner. The National Institutes of Health is the largest source of medical research funding in the world, and our procedures should be based on theirs.

It is satisfactory to accept short, less fully developed, sole source proposals for small ($2-$20,000) exploratory (pilot) studies. However for larger, more expensive studies we should carefully develop and disseminate Requests for Proposals (RFPs) that clearly, and in detail, describe the study goals. All qualified research organizations (both public and private) should be eligible to submit a proposal. ATSDR should be encouraged to do so and to use the opportunity to further develop their proposal into a workable plan. Research money is currently very tight, and we should have no trouble attracting a large number of excellent proposals. This nationwide competition will insure that the studies we fund are based on the best research ideas available, employ the best investigators, and make the best possible use of the public funds which are entrusted to us.

The proposals will conform to a published guideline and consist of a "technical" and a "business" proposal. Those sections include:

WORK PLAN

- Objectives: including overall objectives and specific accomplishments, a rationale for the study plan, and a review of comparable work in progress and completed elsewhere which is relevant to this study and the proposed approach.
- Approach: clearly outline the plan of work, research phases, and probable outcomes of the proposed approaches.
- Methods: detailed description of methodologies to be used, the investigators experience with each, areas of anticipated problems, and extra expenses which are anticipated.
- Schedule: for completion of the work phases.
- Personnel: describes the experience and qualifications of the personnel who will work on the program, and their experience with similar studies. Includes the percentage of their time which will be spent on the study, their titles, and their duties. Consultants must submit letters of commitment and information on the expertise which they will provide. CVs (resumes) are required for all key personnel, as well as a summary of their current and proposed activities

COST AND PRICING DATA:

- Direct labor hours, monthly including rates by category, with key personnel listed individually.
- Materials: A summary of all items to be purchased and the basis for their price.
- Subcontract Items: Include parts and services, with a commitment letter and cost proposal from each contractor..
- Fringe Benefits: Fringe benefits should be shown as a separate line item. Include the method used for their calculation and the organizations guidelines.
- Indirect Costs: Indicate how these costs are calculated, and provide a basis for evaluating their reasonableness.
- Special Equipment: If the proposal includes the purchase of any equipment list its description, price, quantity, and the basis for it's price.
- Travel: provide the overall cost, including destination, duration, purpose, per diem, and the basis for cost estimates.
- Other: List all other costs not otherwise included (such as consultants, computer services) .

The submitted proposals will be evaluated based on the quality of their scientific and technical proposals, and the qualifications of the investigators. Each proposal will receive a score, as is done in NIH study sections. Proposals in the competitive range will be subjected to a cost analysis that includes an evaluation of the cost effectiveness of the proposal, past performance of the investigators and their ability to complete the work on schedule.

The contract recipient will submit quarterly and annually reports, as well as a final report. Funding will be awarded for one year, with continuations contingent on acceptable performance and adherence to schedules.

To award millions of dollars of Navy funds for Epidemiology research without going through this process would be an abrogation of our professional and financial responsibilities.

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VII. Recommendations.

The evidence associating TCE and other VOCs with CL is not strong. Nevertheless, if a population of military dependents was exposed at Camp LeJeune then we should examine the possible effects of the VOCs if a workable study can be designed.

However, until there is any evidence of an increased risk of CL in this population it would not be prudent to spend millions of dollars on a large scale study.

- Accordingly, pilot studies should be conducted to determine if there was an excess of CL at Camp LeJeune. The North Carolina Cancer Registry began in 1987 and received good cooperation from the military hospitals. The California Cancer Registry (the location of most marine personnel) had 85% coverage by 1985. Names of the children in the exposed populations (in the proper age range) should be matched against theses registries. This will provide very limited coverage of the Camp LeJeune population, but should give an indication of any large CL excess. If relevant hospital records (esp. pathology) exist they should be examined at the local military hospitals and at Bethesda. Military physicians who served the Camp Lejeune population should be contacted and asked about their recollections of CL. These pilot studies would cost only a small fraction of the cost of the proposed ATSDR study.

Has there really been a high rate of Leukemia cases?

- If there is evidence of an increase in CL at Camp LeJeune the Armed Forces Epidemiology Board should be asked to offer their opinion on the feasibility of conducting a large study in this population, given the known problems.

90 thru Armed Forces Epidemiology Board 1st

- If they recommend a study, we should develop and circulate a RFP. If the expertise to do this is not currently available in house then we should contract with NIH to provide training to NEHC personnel so that we are able to develop them. We can contract with NIH to develop the RFPs until we are able to do so.
- An investigator should then be selected, funded, and monitored based on the criteria listed in section VI.

Complete record

☐ Citation 1

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Authors
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Title
Elevated incidence of childhood **leukemia** in **Woburn**, Massachusetts: NIEHS Superfund Basic Research Program searches for causes.

Source
Environmental Health Perspectives. 103 Suppl 6:93 8, 1995 Sep.

Abstract
Between 1966 and 1986, the childhood **leukemia** rate in **Woburn**, Massachusetts, was 4-fold higher than the national average. A multidisciplinary research team from MIT, which is being supported by the NIEHS Superfund Basic Research Program, has explored the possible importance of a temporal correlation between the period of elevated **leukemia** and a previously unrecognized mobilization of toxic metals from a waste disposal site in north **Woburn**. Residents of **Woburn** may have been exposed to arsenic (70 micrograms/l) and chromium (240 micrograms/l) at levels in excess of federal drinking water standards (50 micrograms/l for each metal) by consuming municipal groundwater contaminated with these metals. Research is currently underway a) to elucidate the mechanisms and the pathways by which these metals were transported from the waste disposal site to the drinking water supply; b) to determine the identity of the principal human cell mutagens in samples of aquifer materials collected from the site of the municipal supply wells; and c) to measure the extent of exposure and genetic change in residents who consumed the contaminated well water.

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Camp LeJeune - Childhood Leukemia Study Proposal

Purpose:

The purpose of the proposed study is to investigate the potential relationship between exposure to Volatile Organic Compounds (VOCs) in drinking water and childhood leukemia (CL) at the U.S. Marine Corps Base Camp LeJeune, Jacksonville, North Carolina. A secondary objective of the proposed study is to investigate the potential relationship between VOCs in drinking water and birth defects in this population.

Rationale:

CL is the most common cancer that occurs in childhood (*1*), and is of tremendous public health and public concern. There is limited evidence that exposure to VOCs such as trichloroethylene (TCE) in drinking water may be strongly associated with CL (*2*). ATSDR recently constructed a cohort of approximately 6,000 infants exposed to VOCs in drinking water during gestation and 6,000 births that were not exposed to VOCs for a study of pregnancy outcomes at Camp LeJeune. This existing database presents a unique opportunity to examine this potential association in a cohort of moderate size where exposure is relatively well-defined. Tracing the cohort will also allow us to identify any children that were diagnosed with birth defects, but because of the very small number of specific birth defects expected, this is only a secondary objective of the proposed study.

Study Overview:

Proposed is a nested case-control study of childhood leukemia (CL) and birth defects at Camp LeJeune. This study would occur in three phases. In phase I, an attempt would be made to locate as many of the children born to base residents between 1968 and 1985 as possible. During this phase, a brief screening interview would be conducted to identify potential cancer and

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birth defect cases. In phase II, an attempt to verify reported CL and birth defect cases would be made by reviewing medical records of self-reported or parent-reported cases. In phase III, verified cases and a random sample of 100 non-cases would be interviewed in detail to obtain data on potential confounding factors. Additional information regarding proposed data collection methods follow.

Background:

The US Marine Corps Base at Camp LeJeune (MCB Camp LeJeune) is located in Jacksonville, on the eastern coast of North Carolina. Recently, ATSDR documented trichloroethylene (TCE), tetrachloroethylene (PCE), and 1,2-dichloroethylene (DCE) in water systems supplying two different family base housing areas at Camp LeJeune. The estimated number of infants born to residents living in each housing area receiving contaminated water, a list of contaminants, and contaminant levels are summarized in Table 1. Each of the affected housing areas received water containing a mixture of many contaminants, a phenomenon noted with almost every population exposed to contaminants released from hazardous waste sites.

The estimated number of infants in each housing area was determined by ATSDR during a detailed study of late pregnancy outcomes on the base, and a database now exists containing infant, mother and father's names, address at birth, and date of birth for all infants born to residents of base family housing between 1968 and 1985. This previous study identified residents of base family housing based on mother's residence at birth as reported on the birth certificate. For most births, this address was validated using base family housing records. The earliest births in the study occurred in 1968, the first year that birth certificates were computerized in North Carolina. The latest births studied occurred in 1985, the last year that contamination was detected

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at the base. While the pregnancy study, now being completed, was useful in addressing questions related to some late pregnancy outcomes, questions persist about other health effects that may have occurred from this exposure including cancer and birth defects. The existence of this database presents a unique opportunity for continued research into the health effects of VOCs in drinking water, as well as to answer lingering questions about the health among residents at Camp LeJeune.

Childhood leukemia describes a disease process in which white blood cells accumulate, but fail to reach a state of functional maturity. This leaves the individual susceptible to infection, hemorrhage, and inadequate cellular nutrition (*3*). Leukemia has annual incidence of 7.1 per 100,000 among children 0-4 years old and declines to about 2.1 per 100,000 at ages 15-19 years (*4*). Five-year survival rates have increased substantially between 1974 and 1990. However, about one-third of children under 10 and about half of children over 10 still die from the leukemia within 5 years (*4*).

There are few known risk factors for leukemias and those that have been identified appear to explain only a small fraction of leukemia incidence among adults or children (*1*). However, as Sandler (*5*) has argued, variation in leukemia incidence across gender and race in the United States, and between developing and undeveloped countries, supports at least some role for the environment in the etiology of leukemia (*5*). Some of the factors that may potentially increase the risk of CL are: electromagnetic fields, viruses, and consumption of n-Nitroso compounds (*5*).

PCE and TCE, which are metabolized to a common substance, trichloroethane (TCA), are both considered to be probable human carcinogens by the International Agency for Research on Cancer (IARC) on the basis of animal testing (*6-7*). However, IARC considers the human evidence to be too limited to draw definitive conclusions. Some studies of occupational exposures

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to solvents, including PCE and TCE, have noted associations with leukemia and/or non-Hodgkin's lymphoma incidence (*8-9*) or mortality (*10-11*), but these studies did not include large enough groups of pregnant women to address the issue of cancer in offspring exposed *in utero*. A small study of the children of women who owned laundry or a dry-cleaning facility at the time of conception revealed a strong association (OR = 3.7) between occupation and incidence of any childhood cancer. However, because there were only 6 cases, this analysis was not broken out by cancer type (*12*).

Six studies, two in New Jersey and four in Massachusetts, have been conducted of PCE and/or TCE contaminated drinking water and leukemia or non-Hodgkins lymphoma (*2,13,14,15,16,17*). Three of the six studies are analyses of the same TCE-exposed community, and differed only in their details. Each of these six studies, summarized in Table 2, have noted associations between VOCs in drinking water and the incidence of leukemia, although in the New Jersey studies, excesses were limited to specific cell-types and were noted among females only.

Only the three studies in Woburn, Massachusetts focused specifically on leukemia in children. In 1979, two wells supplying water to east Woburn were found to contain approximately 267 ppb TCE and 21 ppb PCE. As summarized in Table 2, the most recent study in this series noted a very strong association between TCE exposure during gestation and CL (OR = 8.3 95% CI: 0.7-95). Moreover, the association was driven by cases which would have received the highest percentage of water from the contaminated wells (OR = 14.3 [0.9-225]). A weaker association was observed when exposure was examined from 2 years prior to conception through age of diagnosis (OR 2.4 95% CI: 0.5, 10.6). The major strengths of this study were good ascertainment of cases, a systematic model for defining exposure, and careful attention to the

timing of exposure. The major weakness of the study was the small sample size which was limited by the total number of cases in Woburn. Moreover, despite the efforts made to model exposure, the year when exposure first began was not known, and the concentrations of contaminants that would have been present in drinking water was modelled based on a minimal amount of data. In addition, because so little is known about the causes of CL, it is not known what potential confounders may have been overlooked. However, the likelihood that an unidentified confounder could create such a strong association is unlikely. Moreover, after 18 years of elevated CL incidence, CL rates reverted to expected in Woburn, approximately 8 years following the closure of the well. This would appear to be an appropriate lag time for CL. The previous investigations at Woburn (*13,14*) found approximately a 2-fold increase in risk, rather than an 8-fold to 14-fold increase, which probably reflects the less specific exposure window (i.e. from birth to diagnosis) in the earlier investigations.

Although it did not focus on CL, a study conducted by Cohn *et al.* (*16*) in New Jersey also noted that CL incidence, particularly acute lymphocytic leukemia (ALL) incidence, was elevated. However, the association between TCE and ALL was only observed in female children but not male children (*16*). Conversely, at Woburn, excesses in leukemia incidence were not limited to ALL and were greater in male children than female children *(2,13,14)*. Given the small numbers, it is difficult to evaluate how important these inconsistencies are.

There have also been suggestions that VOCs such as PCE and TCE may cause birth defects (*13,18,19,20*) although the associations noted were much weaker than for VOCs and CL. Moreover, public concern regarding the effects of these solvents on birth defects is very high.

Methods:

As summarized above, the proposed study would be conducted in three phases. During phase I, we will attempt to locate the members of the cohort identified in our birth database. Between 12 and 30 years have elapsed between birth and the time that we will attempt to locate this group. Tracing will present quite a challenge, because the current database does not contain social security number for the infants born at Camp LeJeune or for their parents. In addition, the database contains an age of each parent at the time of the infant's birth, but not exact birthdays for the parents. Therefore, we will attempt to reduce the number of individuals who must be traced by widely advertising our desire to locate individuals who were born, or whose children were born, at the USMC Camp LeJeune between 1968 and 1985 in publications targetting military personnel. A toll-free number will be established for respondents to provide their name and phone number and indicate their willingness to participate in a health study. A brief screening questionnaire would be used for the following purposes:

(1) to confirm the names of children born on base, their dates of birth, and dates and location of residences on base at the time of each birth;

(2) to determine the vital status of each child and the availability of his/her parents for interview;

(3) to determine whether or not each child had been diagnosed with cancer or birth defects before age 20 and ascertain, to the best of the respondent's knowledge the type of cancer and birth defect diagnosed;

(4) to invite callers to participate in the proposed ATSDR study as 'recruiters'. Recruiters would be asked to disseminate information about ATSDR and the health study to previous

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base residents who may not have seen our advertisements. This would not violate confidentiality since ATSDR would not ask the caller for particular names, nor follow-up with them regarding their recruitment activities. However, it may greatly expand the audience that receives information regarding the proposed study.

If an 80 percent or greater response rate is not acheived through publicity, the remaining children or their parents will be traced through consultation with the Navy (which may have information as to each parent's most recent duty station) and by using services such as Equifax.

Conduct of phases II and III would be contingent on locating a large and representative proportion of the cohort in phase I, as well as the identification of sufficient numbers of cases to complete an acceptable study. We will assess the representativeness of the cohort that is located using demographic characteristics available from the late pregnancy outcome study including race, parity, military rank, and mother's education and age at birth.

In phase II, an attempt to verify reported CL cases would be made by reviewing medical records of self-reported or parent reported cases. Cancer cases for which the organ system was not specified would also be verified to determine the organ system affected. Relevant medical information such as histologic type would also be obtained at this time.

In phase III, the parents of verified cases and the parents of a random sample of non-cases, frequency matched at a rate of 5:1, would be interviewed more completely to assess information about exposure, such as significant time periods during pregnancy spent away from Camp LeJeune and bottled water use, and potential confounders such as parental occupation, smoking status, and service in Vietnam. Interviews would be conducted over the telephone. Odds ratios and 90% confidence intervals for exposure to VOCs in drinking water would be computed for all CL, and

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when possible, for histologic subtypes. Because the number of expected cases in both the exposed and unexposed groups is small, standardized incidence rates would also be computed for the exposed cancer cases compared to an external comparison group, such as CL cases in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) registry. This latter comparison group, while possibly less comparable than the unexposed cohort born at Camp LeJeune, would provide greater power to detect a statistically significant difference between exposed and comparison groups, and would place CL rates in the exposed cohort within a national context.

Sample Size Calculations:

A sample size worksheet is included as Table 3. With a 5:1 matching scheme, the proposed internal comparison group analysis would have 80% power to detect a 5 fold or greater increase in rates of CL, using a one-tailed alpha of .05 (*21*). The proposed analysis using an external standard would have sufficient power to detect a 3 fold or greater increase in rates of CL, using a one-tailed alpha of .05 (*22*). Both power calculations are based upon the assumption that approximately 10,000 of the 12,000 infants (83%) whose parents lived in family base housing at Camp LeJeune when they were born between 1968 and 1985 would be located, and that half of these infants would have resided in exposed housing areas.

The magnitude of associations observed between TCE and PCE exposure and birth defects is much weaker than the magnitude of association observed between these VOCs and CL. Therefore, the power to detect such associations would be weaker. However, the added cost of investigating birth defects once the cohort has been reconstructed would be minimal, and of sufficient interest to be worthwhile.

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Strengths and Limitations:

There are several important strengths of the proposed study. The first is the existence of a database from which can be reconstructed a cohort that was very likely to have been exposed *in utero* to a variety of VOCs in drinking water. Using this database, a representative sample of the exposed population should be identifiable. Moreover, since advertisements will be based on whether individuals were born in base housing, and will not specify which housing areas were exposed, it is hoped that differential participation by exposure will be minimized. In addition, the existing database already contains valuable information about residential history from housing records which can be compared with parental reports of residence. Realistically, 6,000 infants with similar in utero exposures is about as large a population as one would be able to locate in most situations where drinking water contamination has occurred substantially above current drinking water standards. Hence, it could help us to answer questions about CL in this population, and also about the risks of CL in the many smaller populations of individuals where exposure to VOCs through maternal consumption of drinking water may have occurred in utero.

The major limitation of the proposed study is the low study power, such that only very strong associations between exposure and CL will be detected. However, the study power is great enough to detect statistically significant results of the magnitude of those observed at Woburn. Moreover, even findings that are not statistically significant can provide information on the most likely range of values for the association between the exposure and outcome.

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Table 1. Summary of exposure groups and the estimated concentrations of volatile organic compounds in drinking water.

Exposure Group	Exposed Housing Area	Number of Infants	Contaminants detected	Estimated contaminant levels (in ppb)	Period of Exposure
PCE exposed	Tarawa Terrace	6,362	Tetrachloroethylene Trichloroethylene 1,2-Dichloroethylene	215 8 12	1958-Feb 1985
TCE exposed	Hospital Point	32	Trichloroethylene Dichloroethylene Benzene Methylene chloride Vinyl chloride	900-1400 321-407 35* 54 3†	? - Feb 1985 (Activities began in 1940s)
Unexposed***	Midway Park, Berkeley Manor, Rifle Range, Courthouse Bay, Watkin's Village, Paradise Point	5,898			

* Estimated assuming a dilution factor of 20 from sampling data for well 602.

† Detection limit was 10 ppb.

*** Infants were excluded from this group if gestation occurred in their housing area during a 12 day exposure period in 1985

Study Location and Maximum VOC Concentrations Observed in Drinking Water *(Reference)*	Study design and sample size	Odds ratio [95% Confidence Interval] (# of cases) or other results
Woburn, Massachusetts *(2)* Trichloroethylene 237 ppb Tetrachloroethylene 21 ppb	Matched case-control study. 19 incident childhood leukemia cases born 1969-1989 and diagnosed while residing in Woburn. 37 controls selected from school records for the Woburn school district, and on age, race, sex and residence in Woburn on date of diagnosis. Exposure was based on a model for distribution of different water wells to different areas of Woburn, and the duration of residence during different critical periods.	Exposure during pregnancy None 1.0 (9) Any 8.3 [0.7, 95] (10) Least 3.5 [0.2, 58] (3) Most 14.3 [0.9,225] (7)
Woburn, Massachusetts *(13)* Trichloroethylene 237 ppb Tetrachloroethylene 21 ppb	Cumulative and ever-never exposure to contaminated wells was assessed 20 incident childhood leukemia cases diagnosed between 1969 and 1983, and compared to the rate expected based on exposure rates in 164 healthy controls. Exposure was based on a model for distribution of different water wells to different areas of Woburn, and the duration of residence in Woburn throughout the child's life.	Ratio of observed ever exposed/ expected ever exposed: 1.8 (p = .02) Ratio of observed cumulative exposure score/ expected cumulative score:2.0 (p = .03)
Woburn, Massachusetts *(14)* Trichloroethylene 237 ppb Tetrachloroethylene 21 ppb	Incidence of childhood leukemia between 1969 and 1978 in Woburn was compared to the expected incidence based on the Third National Cancer Survey. The geographic location of cancers was also assessed.	Incidence in Woburn 2.3 times expected (p=.007) (12 cases) Incidence in East Woburn 7.5 times expected (p = .0002)
Barnstable County, Massachusetts *(15)* Tetrachloroethylene 7750 ppb	34 incident leukemia (all ages) cases and 737 controls during 1983-1986 were studied. Exposure dose was modelled based on information regarding PVC piping use in the water system. Information on demographic characteristics, residential history, smoking, medical and occupational history, bottled water consumption, and bathing habits was also collected.	Exposure category Any 2.0 [0.7-5.5] (7) Above 90th percentile 5.8 [1.4-25] (2)
New Jersey *(16)* Trichloroethylene > 5 ppb Tetrachloroethylene > 5 ppb	Registry-based study of leukemia and non-Hodgkins lymphoma of all ages in 75 municipalities. Mean VOC concentrations were estimated for each distribution system based on water samples taken in 1984 and 1985. Cancer incidence between 1979-1987 were compared in municipalities that had different levels of VOCs in public drinking water supplies.	TCE and childhood ALL in females < 1 ppb 1.0 > 5 ppb 3.3 [1.3, 8.3] (6) TCE not associated with ALL in males PCE not associated with ALL in either sex
New Jersey *(17)* TCE 46 ppb PCE 16 ppb	Ecologic study based on leukemia incidence data for all ages from cancer registry for the years 1979-1984. Observed rates were compared with expected in exposure categories defined by mean chemical-specific concentration of VOCs.	TCE in females 1.7 [not reported] PCE in females 1.7 [not reported] No association between exposure and leukemia in males.

L= acute lymphocytic leukemia

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Table 5. Sample Size Worksheet

Target: Identify 10,000/12,000 (83%) births. 5,000 will be unexposed.

Age	Baseline Incidence rate	Person-years*	Expected Unexposed cases	Expected Exposed cases (If no elevation in risk)
0-4 years	7.1/100,000	25,000	1.8	1.8
5-9 years	3.9/100,000	25,000	1.0	1.0
10-14 years	2.3/100,000	24,510	0.6	0.6
15-19 years	2.1/100,000	11,550	0.2	0.2
All ages:			3.6	3.6

Power Calculation Using Internal Comparison Group

Odds Ratio	Expected Exposed Cases	Power to detect when one-tailed alpha = .05
2.0	2(3.6)= 7.2	.12
3.0	3(3.6)= 10.8	.57
5.0	5(3.6)= 18	.79

Power Calculation Using External Comparison Group

Odds Ratio	Expected Exposed Cases (When risk does not differ from baseline)	Power to detect when one-tailed alpha = .05
2.0	3	.39
3.0	3	.79
5.0	3	.99
2.0	4	.41
3.0	4	.84
5.0	4	1.0

Person-years declines because some cohort members will be younger than 19.

Medical Records Review:

In FY 1998, ATSDR plans to review between 400 and 600 prenatal care medical records for mothers included in the Camp LeJeune Pregnancy Outcome Study. In FYs 1995-1997 ATSDR conducted a study of birth outcomes in the infants of mothers exposed to VOCs during pregnancy. Results contained in the Interim Report from this study indicated an association between PCE exposure and small for gestational age in two potentially susceptible subgroups: mothers with previous fetal losses and mothers 35 years of age and older. As concluded in the Interim Report, these results merit further scrutiny.

Reviewing prenatal care records would be useful to improve upon the information available to us from the birth certificate. One critical source of information available on the medical record is an expanded maternal pregnancy history. Each birth certificate contained information on previous fetal deaths for all gestational ages combined. However, fetal deaths occurring at early gestational ages (miscarriages) have a different etiology than fetal deaths occurring at late gestational ages (stillbirths). It is also not clear whether fetal deaths at these different gestational ages were reported more or less completely. Unlike the birth certificate, the medical record indicates whether the fetal losses were stillbirths or miscarriages. Information regarding maternal medical conditions such as diabetes and hypertension, maternal height, and maternal weight gain would also greatly enrich the existing data for both the older mothers and the mothers with histories of fetal death. Given the adverse findings for women in these clinically susceptible subgroups, the modest cost involved in abstracting medical records from a sample of women would be quite valuable.

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Proposed Budget and Timeline:

Fiscal Year 1998
Phase I

Location of Cohort	
Advertisements	$ 40,000
Toll-free Number	$ 20,000
Screening Phone Calls (12,000 calls)	$ 430,000
Participant tracing (5,000 records)	$ 770,000
Data entry and data management phase I and II	$ 240,000
Medical record review	$ 100,000

Fiscal Year 1999
Phase II

Verification of medical diagnosis (100 records)	$ 15,000

Phase III

Interviews – 200 (120 controls up to 80 cases)	$ 30,000
Data entry and data management	$ 10,000
Data analysis and reporting	$ 135,000
Total Fiscal Year 1998	$ 1,600,000
Total Fiscal Year 1999	$ 190,000
Total Fiscal Year 1998 and 1999	$ 1,790,000

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