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Supporting Statement

Epidemiologic Study of the Health of Vietnam Veterans

Centers for Disease Control

November 1983

Contents

Supporting Statement

A. Justification

1. Background

During the past several years, a large number of Vietnam veterans have come to believe that they have an unusually high frequency of certain illnesses. Much of their concern stems from presumed exposure to Agent Orange, and to dioxin, a contaminant present in Agent Orange. (Dioxin has been demonstrated to be carcinogenic and teratogenic in laboratory animals). In addition to cancer, veterans have complained of other adverse health effects including neurologic disorders, reproductive problems, and infections. Unfortunately, there is little objective evidence regarding the health of Vietnam veterans relative to other men of similar age.

In recognition of this lack of information, Public Law 96-151 (Attachment 1) required that the Veterans Administration (VA) conduct an "epidemiologic" study of U.S. veterans to assess the possible health effects of exposure to herbicides and dioxin during the Vietnam War. Public Law 97-72 (Attachment 2) expanded this mandate to include the study of other environmental exposures which may have occurred in Vietnam. In January, 1983, the responsibility for design, conduct, and analysis of studies responsive to these laws was transferred from VA to CDC by an Interagency Agreement.

2. Purpose

A major concern of Vietnam veterans is that they are at high risk for a variety of diseases. The cause of this putative high risk is generally suspected to be exposure to Agent Orange and other herbicides, but there is also concern that there may have been other factors incidental to Vietnam service which conferred an increased risk. Collection of necessary information and performance of CDC's proposed studies should permit an assessment of the validity of both the general and some of the specific concerns. Without these studies the veterans' concerns cannot be addressed and the Congressional mandate cannot be fulfilled.

This submission is for an "Agent Orange" (A.O.) Study, a "Vietnam Experience" (V.E.) Study, and a "Selected Cancers" Study (Attachment 3, Protocols). The Agent Orange study is a cohort study designed to try to determine whether or not the health experience of Vietnam veterans exposed to Agent Orange differs significantly from that of Vietnam veterans not so exposed. This study will involve three cohorts of some 6000 men each. Two of the cohorts will be drawn from a random sample of combat battalions which served in the III Corps tactical area of Vietnam in 1967-68. This location and time represent an area and period of heavy Agent Orange use.

A third cohort will be selected by a different method. Areas for which there is no evidence of herbicide use prior to 1969 will be identified and a list of units which served only in those areas during 1967-68 will be compiled. From this list a sample of units will be drawn and subjects for the third cohort will be selected from that sample.

The Vietnam Experience Study will involve two cohorts of 6000 subjects each. It is designed to evaluate whether veterans who served in Vietnam are at greater risk for certain adverse health outcomes than are their counterparts who served elsewhere. Selection of subjects will be based on review of systematically chosen personnel records located at the St. Louis records center. Both cohorts will consist of Army first term enlistees or

draftees who served in the non-officer ranks between 1966 and 1971. The first cohort will be those selected individuals who served only in the U.S. and Vietnam; the second cohort will be comprised of three groups: 1) service in U.S. only; 2) service in U.S. and Europe; 3) service in U.S. and Korea. A random subset from each of the five study cohorts will be selected to participate in medical, psychological and laboratory evaluation. The goal will be to complete examinations on 2000 men per cohort.

The Selected Cancers Study (SCS) is a population based case control study designed to determine whether men who served in Vietnam are at increased risk of developing soft tissue sarcoma, lymphoma, liver, and nasopharyngeal cancer. Cases will be men with birthdates 1933-53 and identified with one of the selected cancers from July 1, 1984 to June 30, 1988. Cases will be identified and interviewed by cooperating Surveillance, Epidemiology, and End Result (SEER) Centers. These centers are population-based cancer registries sponsored by the National Cancer Institute (NCI). Controls will be selected by the random digit dialing method and matched to cases by age, sex, and race. Interview of controls will also be performed by the SEER Centers.

Subjects in all three studies will be interviewed to collect pertinent information. For the Agent Orange and Vietnam experience studies, this will include: sociodemographic data, medical history, environmental and occupational exposure information, and military history. In addition to these elements, participants in the Selected Cancers Study will be questioned regarding family history of cancer. A.O. and V.E. study interviews will be conducted by telephone, and will be supplemented by in-person contact should pilot testing indicate that participation is suffering because too few study subjects can be reached by telephone. All SCS interviews will be conducted face to face. Estimated response time for each interview is one hour per subject.

3. Information Technology

CDC proposes that a "computer assisted telephone interviewing" (CATI) system be employed. The quality control advantages provided by such a system serve to reduce respondent burden by speeding administration of the questionnaire and eliminating call-backs because of interviewer failure. Furthermore, by its nature telephone interviewing is less intrusive than is an in-person technique. The in-person technique was chosen for the Selected Cancers Study because the SEER Centers are familiar with that approach and the logistics of establishing a CATI system in multiple sites are unmanageable. Such an approach would also be extremely expensive.

4. Identification of Duplication

The United States Air Force has recently completed a cohort study of the air crews and support personnel involved in aerial spraying of Agent Orange in Vietnam ("Operation Ranch Hand"). This study will provide extensive data regarding health effects resulting from exposure to Agent Orange. However, neither the exposures nor the personnel involved in the Air Force study are representative of the ground forces which are the focus of CDC's proposed studies. Furthermore the Air Force study made no attempt to investigate the health effects of the general "Vietnam Experience."

In December, 1980, the Veterans Administration (VA) contracted for a "Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins." The report on that review was delivered to VA in September, 1981. Volume I of that report ("Analysis of Literature") stated that a gap in existing information existed in that: "Human health effects from use of defoliants in Vietnam have not been systematically documented." The Agent Orange Study proposed by CDC is designed to help close this gap.

The questions of adverse health effects stemming from the general experience of service in Vietnam as well as possible excesses of soft tissue sarcoma and lymphoma among Vietnam veterans have not been previously addressed in a scientifically rigorous fashion. The "Selected Cancers" and "Vietnam Experience" studies proposed by CDC represent the first efforts to answer these questions and fulfill the Congressional mandate to conduct epidemiologic studies of environmental exposures which may have ocurred in Vietnam.

5. Use of Existing Data

Existing data cannot be modified to completely satisfy the requirements of the Agent Orange, Vietnam Experience, and Selected Cancers studies. In the case of the Soft Tissue Sarcoma and Vietnam Experience studies, as previously stated, the data simply do not exist. Regarding the Agent Orange Study, most of the data bearing on this question are drawn from occupational settings, and most reports and studies of workers exposed to TCDD (dioxin) are descriptive. Additionally the age/race/ethnic composition of the groups of factory workers exposed is not comparable to that of American ground forces in Vietnam in 1967-68 and the extremely heavy exposures experienced in industrial accidents are not typical of the exposures of ground troops in Vietnam. The Veterans Administration has been evaluating Vietnam veterans for signs and symptoms of adverse health effects attributable to phenoxyherbicide and dioxin exposure. Data collection began as the "Agent Orange Registry" in 1978. Any veteran who was concerned about the health effects of Agent Orange could report to a V.A. hospital for a complete medical and exposure history, physical examination, and selected laboratory tests.

By September 1983 over 110,000 veterans had been evaluated and summary results had been published by the V.A. Although the quality of the evaluation received by this extremely large group of veterans is not in question, the data from the VA Agent Orange registry are not suitable for CDC's epidemiologic study because the sample was self-selected. In order for CDC's study to be valid, a random sample must be evaluated to assure that results are not affected by selection bias.

6. Small Business

Data collection will involve only individual subjects and controls selected according to the sampling procedure described in section B of this justification; no portion of the collection effort will involve small businesses or similar entities.

7. Consequence of Less Frequent Collection

The data collection proposed herein is a one-time per subject effort; follow-up of these study and control groups is expected to include medical examinations of a randomly selected subset of subjects and periodic ascertainment of vital status of respondents. Vital status determinations can probably be accomplished by means of existing records systems.

8. 5 CFR 1320.6

It will be necessary to compensate the participants in the medical examination component of the study for their time, if we are to achieve a participation rate high enough to produce valid results. The examination itself will require at least two days, and may well extend into a third. Travel to and from the examination site will require one day each way; thus the average time commitment per subject for examination will be 4-5 days.

The length of time involved makes it impossible to schedule examinations entirely on weekends or other routine "off days," and many subjects will have employment which does not provide paid time off for

purposes such as this. Further, the number of subjects involved (10,000) makes it impractical for the Government to try to make individualized leave arrangements for each participant. The only option available to prevent the medical examination from being a prohibitive financial burden on the less well-to-do participants (thus producing a biased sample) is to pay a stipend to each participant.

The Air Force in its Ranch Hand II Study compensated its participants at $100/examination day, and succeeded in attaining a participation rate of 95+%. Participation at a similar level is highly desirable, especially when one is trying to detect rare events (e.g. certain forms of cancer). If CDC is to hope to approach the participation rate achieved in the Air Force study, it is clear that some similar compensatory arrangement will be required.

9. Consultation

In developing this submission, CDC has had a number of "outside" consultations. These have included scientific reviews and contacts with other interested parties, principally veterans groups. In May, 1983, scientific reviewers were sent copies of the study protocols and invited to comment as were representatives of several veterans groups. In addition to the protocol review, CDC has conducted update briefings with veterans' representatives. The last such briefing was on August 31, 1983.

The following is a list of scientists and veterans' representatives with whom CDC has worked.

a) Scientific and/or Government Reviewers:

1. Agent Orange Working Group
   Science Panel

2. Howard W. Ory, M.D.
   Deputy Director for Research, EPO, CDC

3. Richard Dicker, M.D.
   Medical Epidemiologist, EPO, CDC

4. Dave Culver, Ph.D.
   Hospital Infections Program, CID, CDC

5. Claire Broome, M.D.
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6. Richard Remington, Ph.D., Chairman
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15. Claire O. Leonard, M.D.
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17. Mr. Theodore P. Sypko
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18. Mr. John F. Terzano
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19. Mr. Monte C. Throdahl
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20. H. Michael D. Utidjian, M.D.
    Corporate Medical Director
    American Cyanamid Company
    Wayne, NJ 07470

21. G. Comstock, M.D.
    Johns Hopkins Medical Institutes

22. R. Hoover, M.D.
    NCI

23. R. Monson, M.D.
    Harvard University

24. J. Moore, M.D.
    NIEHS

25. P. Sartwell, M.D.
    Formerly of
    Johns Hopkins Medical Institutes

26. I. J. Selikoff, M.D.
    Mt. Sinai Hospital (N.Y.)

b) Veterans' Representatives

1. Mr. John Sommer
   The American Legion

2. Mr. John Terzano
   Vietnam Veterans of America

3. Mr. Fred Juarbe
   Veterans of Foreign Wars

4. Mr. Charlie Thompson
   Disabled American Veterans

5. Lewis Milford, Esq.
   National Veterans Law Center

6. Mr. Fred Mullen
   Paralyzed Veterans of America

7. Mr. Noel Woosley
   Am Vets

8. Mr. Jack P. Garver
   American Red Cross

9. Mr. Wilburn Long
   Blind Veterans of America

10. Mr. Frank Weil
    American Veterans Committee

11. Mr. Dick Gallant
    Military Order of the Purple Heart

12. Mr. Dick Johnson
    Non-Commissioned Officers' Association

13. Mr. Max Beilke
    National Association for Uniformed Services

Comments, recommendations, and criticisms received from reviewers are addressed in the final version of the study protocol.

10. Confidentiality Assurance

The Acting Director, National Center for Health Statistics, delegated to the Director, CDC, the following authorities under Title III of the Public Health Service Act, as amended, as they pertain to the epidemiologic and statistical responsibilities assigned to CDC.

> Section 304 of the Public Health Service Act (42 U.S.C. 242b), as amended - General Authority Respecting Research, Evaluations, and Demonstrations in Health Statistics, Health Services and Health Care Technology to collect information through health statistical or epidemiological activities, where such activities of CDC are not duplicative of other activities of the Department, and when the Director, CDC, determines that the authority to give assurances of confidentiality based upon Section 308(d) is necessary for the successful conduct of these statistical and epidemiological activities.
>
> Section 306 of the Public Health Service Act (42 U.S.C. 242k), as amended - National Center for Health Statistics, to collect information through health statistical or epidemiological activities, where such activities of CDC are not duplicative of other activities of the Department, and when the Director, CDC determines that the authority to give assurances of confidentiality based upon Section 308(d) is necessary for the successful conduct of these statistical and epidemiological activities.

Section 308(d) allows an assurance of confidentiality to be authorized for the protection of identifiable information about individuals or establishments.

Approval to give study participants assurance of confidentiality (Attachment 4, Confidentiality Assurances Statement) under these authorities has been requested from the Director, CDC. Verbal approval to assure confidentiality has been given; a copy of the formal authorization will be forwarded on receipt.

11. Sensitive Data

Much of the data to be collected in these studies can be considered sensitive. Questions will be asked regarding race, religion, legal difficulties, employment problems, fertility problems, and illicit drug use. Race and religion information must be collected, because some conditions of interest (e.g. cancer) are not randomly distributed with regard to these factors. Questions about legal difficulties, employment problems and illicit drug use are necessary because veterans groups have suggested that these conditions are in excess among Vietnam veterans; that contention must be evaluated. Finally, information about fertility problems is required because increased rates of infertility and birth defects have been attributed to Agent Orange exposure.

12. Cost to the Federal Government

Conduct of these studies will involve both "in-house" and contract expenses in excess of $73,000,000 over a period of four years. Costs will be borne by the Veterans Administration, and outlays are projected in the following amounts* for the categories shown.

Object Class	1984	1985	1986	1987	Total
1. Personnel	$3,000	3,150	3,300	3,040	12,490
2. Travel/Transport of Persons					
Employee Travel	300	315	330	275	1,220
All Other	60	20	15	10	105
3. Trans. (things)	30	30	10	10	80
4. Commo/Utilities (& other rent)	50	60	60	50	220
5. Printing & Repro.	25	50	50	30	155
6. Contracts	10,576	19,320	19,320	9,660	58,876
7. Supplies & Mtls.	10	10	10	10	40
8. Equipment	25	15	15	15	70
Total	14,076	22,970	23,110	13,100	73,256

*In Thousands

No direct costs will accrue to the study participants. Interviews will be scheduled at times that do not conflict with the particular respondent's work, and participants in the medical examination component of the study will have no out of pocket expenses for travel, lodging, subsistence, or incidentals associated with the examination. The examination itself, of course, will be free to the participants.

13. Respondent Burden

The Agent Orange and Vietnam Experience studies will involve 30,000 respondents (5 cohorts, 6000 subjects per cohort). It is anticipated that 85% of individuals falling into the sample will be locatable and that 85% of those people will agree to interview. Thus, a sample of 8350 subjects will be drawn of whom 7100 should be locatable and 6000 of those interviewable. Average contact time is expected to be about 55 minutes. Contact with refusals will be brief ($\leq$ 10 minutes) while complete interviews may require one hour or more depending upon the extent and complexity of responses.

Interviews will be conducted by telephone on a one time per respondent basis. At least two thousand subjects per cohort will be selected randomly and asked to participate in a thorough medical and laboratory evaluation. Individuals falling into this subset will be contacted a second time to secure their participation in the examination phase of these studies. Burden hours for the Agent Orange and Vietnam Experience are projected as follows:

	1984	1985	1986	1987
Hours	6,000	10,000	10,000	4,000

The Selected Cancers Study will involve approximately 1300 cases and 1300 controls; average interview time for both cases and controls will be one hour. However, the fatality rate for soft tissue sarcoma is quite high, and it may be necessary in some cases to collect information from next-of-kin instead of the affected man. In these situations data collection would be limited to relatively simple items such as whether the man served in Vietnam. Thus, next-of-kin interviews will be extremely brief.

Since the cases of interest are those occurring from July 1, 1984, to June 30, 1988, respondent burden, for both cases and controls, will be spread over four years. Interviews will be conducted by telephone on a one-time per respondent basis; distribution of burden hours is expected to be as follows:

1984	1985	1986	1987
650	650	650	650

Total burden hours for all three studies are:

	1984	1985	1986	1987
Hours	6,650	10,650	10,650	4,650

14. Changes in Burden

At this time there is no cause to expect changes in the estimate of respondent burden. Should field experience suggest an increase or decrease, an amended estimate will be submitted.

15. Project Schedule

CDC will prepare comprehensive reports of the findings for each of the study phases; ideally, major findings will be published simultaneously in peer-reviewed medical journals. Contingent upon necessary funds and positions being available, the following timetable is proposed for the three study phases:

1. May 84 - August 84:	Sample selection & pilot testing for Agent Orange (AO), Vietnam Experience (VE), and Selected Cancers (SC) studies.
2. October 84 - January 86:	AO, VE, and SC main study interviews and exams.
3. January 86 - March 87 :	Complete AO, and VE main study interviews, exams, and mortality data collection. Report findings.
4. March 87 - September 87:	Report SC study data.

B. Collection of Information Employing Statistical Methods

1. Respondent Universe

The potential respondent universe for the Agent Orange Study includes all non-officer single term enlistees and draftees who served in the Army in III Corps in Vietnam in 1967-68. The Vietnam Experience universe is all non-officer single term enlistees and draftees who served in the Army during the period 1966-71. The universe for the Selected Cancers Study is all men with 1929-1953 birthdates who reside in 10 or more SEER areas (NCI, 1981). The probable areas are: The states of Connecticut, Hawaii, Iowa, New Mexico, Utah, and the Commonwealth of Puerto Rico; and the metropolitan areas of Atlanta, Detroit, San Francisco and Seattle.

Numbers of potential respondents, sample sizes, and participation rates are displayed in tables I-V below.

I. Agent Orange Study, Interview Phase

Universe = 200,037* (individuals; 1st Term Army, Non-Officer, 1967-1968)

	Cohort #1	Cohort #2	Cohort #3
Full Sample (#)	8350	8350	8350
Locatable (@ 85%)	7097	7097	7097
Interviewed (@ 85%)	6032	6032	6032

II. Agent Orange Study, Clinical Phase

	Cohort #1	Cohort #2	Cohort #3
Full Sample (#)	2410	2410	2410
Locatable (@ 100%)	2410	2410	2410
Examined (@ 83%)	2000	2000	2000

III. Vietnam Experience Study, Interview Phase

	Cohort #1	Cohort #2
Full Sample (#)	8350	8350
Locatable (@ 85%)	7097	7097
Interviewed (@ 85%)	6032	6032

IV. Vietnam Experience Study, Clinical Phase

Universe = 12,064 (interviewed subjects)

	Cohort #1	Cohort #2
Full Sample (#)	2410	2410
Locatable (@100%)	2410	2410
Examined (@ 83%)	2000	2000

V. Selected Cancers Study

Universe = 2,481,000

	Cases	Controls
Total (4 years)	1228**	1800

* Value was derived by applying the percent of "all Army" assigned to Vietnam in 1967 (18%) and 1968 (21%) to the total number of inductions and first enlistments in those years; 489,389 in 1967 and 533,082 in 1968. Intuitively one would expect "first termers" to be more often assigned to Vietnam than their percentage of "all Army" would indicate; however, no data are available with which this supposition can be evaluated.

** Estimate based on rates of sarcoma, lymphoma, nasopharyngeal, and liver cancers in selected SEER areas.

2. Data Collection Procedures

CDC proposes to limit this study to draftees and single term enlistees in the non-officer ranks who served in the Army; selection will be further limited to those who had only one tour of duty in Vietnam. Exclusion of officers is based primarily on a desire to make the groups as homogeneous as possible with respect to pre-existing demographic factors which could influence health. In addition, the inclusion of officers might require substantially increased record review to assess herbicide exposure potential (see below) because of multiple tours of duty in Vietnam.

Exclusive focus on veterans of the Army is chosen for several reasons. The Army had a much greater proportion of draftees than the other services and it is felt that it is important to include substantial numbers of them in the study. Use of draftees will probably make achieving a balance on such factors as training, military occupational specialities, and pre-existing demographic factors easier. Inclusion of substantial numbers of draftees is also motivated by a desire to try to make an assessment of the possible association between volunteerism and health. (However,such an assessment may not be possible if a large percentage of enlistees joined the Army because they felt that the draft was inevitable.) CDC proposes to exclude the Marine Corps in part because its men were mostly volunteers and in part to limit the amount of records review required to select study subjects (the reasons for this will be better appreciated after the selection process is described). In addition, the AAOTF has worked most extensively with the records of the US Army, has become most familiar with them, and feels most confident about their quality. Moreover, the Air Force did not keep records which allow the daily geographical placement of personnel, and there were rather limited numbers of Navy servicemen who were stationed on land in the Vietnam theatre. Even though all study participants will be males in the non-officer ranks who were in the Army, it is likely that the results will be useful in making inferences about all men who had similar ground experiences and possible herbicide exposures in Vietnam; the same may be said about females if there are no sex-specific effects.

As has been noted previously, there will be three cohorts of men chosen for the Agent Orange study. The first two cohorts, which will differ with respect to the likelihood of exposure to herbicides, will be chosen from III Corps (an area where herbicides were used extensively) during the same period of time, 1967-1968. This will be done in order to make the two as similar as possible with regard to the nature of their service experience -- similar with regard to, for example, type of terrain, indigenous diseases, and intensity of combat. To enhance the possiblity of including soldiers who may have been exposed to herbicides, the men included in these first two cohorts will be selected exclusively from combat battalions. Since these two cohorts will be chosen from an area where herbicides were extensively used, there is potential for exposure misclassification (i.e. some of the supposedly unexposed veterans may in fact have been in contact with herbicide). The third cohort will therefore be chosen from an area where there is good evidence that there was no usage of herbicides. According to the staff of the AAOTF it will probably not be possible to derive this third cohort exclusively from combat battalions.

Selection of veterans to be included in the first two Agent Orange study cohorts will be done by a multi-step review of military records, beginning with the selection of a geographical area of consideration and ending with the choice of individual soldiers. Since many of the proposed procedures are untested, modification may be required after pilot study assessments . In summary, the steps required are:

1) select a geographical area and time of interest - these will be III Corps and 1967-1968
2) determine which of the battalions stationed in III Corps in 1967-1968 have acceptable records
3) choose a random sample of 50 battalions (250 companies) from among all battalions with acceptable records
4) abstract selected companies' locations on one randomly selected day of the week for each of the 104 weeks in 1967-1968
5) using the "Herbs" and "Services Herbs" tapes, score the herbicide encounters of the 250 companies on the 104 days
6) rank the 250 companies with respect to their herbicide encounters
7) choose men for the "likely exposed" cohort from companies at the top of the ranked list and men for the "likely not exposed" cohort from those at the bottom of the list.

The rationale for these steps is presented below.

In order to limit the amount of records review required, the first step is to restrict, on the advice of the AAOTF, the geographical area of consideration to III Corps and the time period to 1967-1968. This time period and area was selected because of a variety of factors, including the number of Ranch Hand missions, the relatively high level of TCDD contamination of the Agent Orange used then, and U.S. troop strength, which was at its peak. The AAOTF has determined that there were about 110-120 Army combat battalions stationed in III Corps during that time (usual battalion strength was 1000). The records of the companies attached to these battalions will serve as the major source of information about troop locations.

The second step in the selection process will consist of a review of GSA documents to ascertain which battalion records appear to have unacceptable time gaps (if gaps appear in battalion records it may be possible to supplement them with division and brigade level records, and this will be done when feasible). CDC does not feel that it is necessarily wise to exclude a unit simply because some of its records are missing -- units with missing records could have had more or less exposure to herbicides than units with complete records. Therefore it is proposed to apply the following criteria regarding records quality: if a battalion has more than 30 contiguous days of absent records or an aggregate of more than 60 days absent records for the time period 1967-1968, the unit will be considered unsuitable for inclusion in the study. If very few units are found to have gaps of this magnitude it is possible that more stringent criteria can be used. For each of the combat battalions located in III Corps in 1967-1968, the AAOTF will summarize the condition of the records as indicated in the GSA documents.

The third step will be the choice of a random sample of 50 battalions (250 companies) from among those which are judged suitable during the second step. Step four will involve abstracting from company records (or battalion records, if necessary) all locations recorded for the selected companies on each day for each of the 104 weeks during 1967-1968. These two sampling steps will be done in order to limit the quantity of records review required, but it should be sufficient to provide a reasonable estimation of the range of herbicide encounters. CDC believes that this is an important issue -- at this point the frequency and nature of troop herbicide encounters is largely a matter of conjecture (aside from the work done by the AAOTF with 2 Army battalions). As noted before, the records available will never permit an unambiguous assessment of exposures, but this approach will help to place a frame of objectivity around the issue, at least for men in Army combat units in III Corps in 1967-1968.

In step five, CDC will check the selected company locations against the locations of herbicide applications as recorded on the "Herbs" and "Services Herbs" tapes. The "Herbs" tape contains computerized records of Ranch Hand missions (time, place, type and amount of herbicide). The National Academy of Science report (1974) on the effects of herbicide usage in Vietnam contains a relatively limited assessment of the accuracy of these records. CDC finds the results of this investigation encouraging, but doubt about accuracy exists in some quarters today. CDC has requested that the National Academy make available the results of other checks which were done at the time, and to look into the possibility of further accuracy checks. The "Services Herbs" tape primarily contains records of non-Ranch Hand herbicide applications (eg, base perimeter sprayings). This set of data has been put together by the AAOTF from a review of a variety of military records; the degree of completeness of the "Services Herbs" data set is unknown.

The number of unit encounters with herbicide applications according to these data sets will be tabulated by at least three systems. The first of these systems will have geometrically progressing scores or weights for various space and time distances and the second will have linear weights. The aggregate scores for these two systems will be based on the products of the time and space scores. The third system, a variant of one proposed by the Department of Defense, will simply count the number of encounters which are at distances of less than 3 days and 2 kilometers. The purpose of these exposure systems is to obtain a spread of unit exposures so that units can be chosen from the top and bottom of the scales. It is desired that the spreads obtained should reflect "meaningful" differences in exposure. Relatively little is known about the environmental fate of herbicides and TCDD, and even less is known about the human pharmacokinetics of these substances. Because of this lack of knowledge, these systems are necessarily arbitrary and this motivates the proposal of three scales. The scorings for the first two systems proposed for preliminary tabulation are indicated below.

Exposure System A

1. Ranch Hand Missions

   a. Regular Missions -- cross-classified by time after mission (<=1 day, score=16; 2-3 days, score=4; 4-30 days, score=2; and 31-59 days, score=1), distance (<=1 km, score=4; 2-3 km, score=2; 4-8 km, score=1), and type of herbicide.

   b. Aborted Missions -- cross-classified and scored as above.

2. Other Herbicide Applications (e.g., perimeter spraying)--for those encounters <= 1 km classified by time and scored as above

Exposure System B.

1. Ranch Hand Missions

   a. Regular Missions -- cross-classified by time after mission (<=1 day, score=4; 2 - 3 days, score=3; 4 - 30 days, score=2; and 31 - 59 days, score=1), distance (<=1 km, score=3; 2 - 3 km, score=2; 4 - 8 km,score=1), and type of herbicide.

   b. Aborted Missions -- cross-classified and scored as above.

2. Other Herbicide Applications (e.g., perimeter spraying) -- for those encounters <= 1 km classified by time and scored as above.

As mentioned before, the various encounters will be weighted by the product of the time and distance scores; each encounter of a unit with a particular herbicide application will be counted in only one time and one distance category. For example, using Exposure System A an encounter with a Ranch Hand mission within 1 day and 1 km would receive a score of 64, as would an encounter with a base perimeter application within 1 day (small bases); an encounter with a Ranch Hand application within 4 - 30 days and 2 - 3 kilometers would get a score of 4. Using the third (modified Department of Defense) system, any encounter which occurs within the 3 day-2 kilometer limit would receive a score of 1. The daily scores determined by each of the three exposure systems will then be summed over the sampled 104 days for each company.

Next, the 250 or so companies will be ranked on their summed encounter scores. If there is good agreement in the rankings provided by the three systems, those at the top of the lists will provide individuals for the "more exposed" cohort and those at the bottom will contribute to the "less exposed" group. If there are substantial disparities in the rankings provided by the three systems then roughly 1/3 of each of the two cohorts will be chosen from the top and bottom of each of the rankings. At this time it is unclear how many companies will have to be selected to provide the requisite number of individuals for these 2 cohorts, but it will probably be on the order of 50 to 60 from the top and a like number from the bottom. If 55 companies each provide 150 suitable individuals this number will allow some loss due to non-participation and yield the number desired for each of the cohorts.

The desire to omit the Marine Corps from this study can now be more easily understood. If Marines were to be included, the records review and other selection tasks to this point would have to be done separately for them because they were largely stationed in I Corps, and this would cause delay.

The next step will be the choice of individual soldiers from the selected units. This process will begin with a review of company morning reports. Individuals who appear to meet the criteria with respect to type of entry into the service (draftee or single term enlistee), are in the non-officer ranks, and whose 1-year Vietnam tour began and ended during 1967-1968 will be considered potentially eligible for inclusion in one of the cohorts. For those who appear to be eligible, the AAOTF will also document their presence or absence with the selected units on each of the days during the 2 year period 1967-1968. Those individuals who were absent from their units for more than 90 days of their scheduled 12 month tours (exclusive of their regular R&R leave) will be considered ineligible for final selection. The AAOTF will also document the reasons for all absences for both the selected men and those men who would be eligible save for their absences. Thus, this process will provide CDC with, inter alia, a measure of combat intensity since absences for reason of casualty will be recorded. Individual personnel folders will be obtained from the St. Louis records center by the AAOTF for soldiers considered eligible. Staff of the AAOTF will abstract certain identifying and service (e.g., military occupational specialty) information from the individual personnel folders and forward the information to CDC on an incremental basis so that it can begin the process of locating the veterans and soliciting their paricipation in the studies. Company records will also be used to document the locations of the selected units on all days during 1967-1968. This information will later be used to classify individual soldiers with respect to exposure to herbicides by a scheme similar to that noted above.

The third cohort for the Agent Orange study will be selected by a different method. Areas in Vietnam where there is no evidence of herbicide usage prior to 1969 will be identified by the AAOTF and a roster of units which served in, and only in, those areas and only in those areas in 1967-1968 compiled. The staff of the AAOTF has suggested that Cam Ranh Bay or Vung Tau might be examples of such areas. Enough units will be randomly chosen from this roster so that the required number of individuals can be included in the study. The eligibility criteria for selecting individuals from within the selected units will be the same as those used for the first two cohorts. The AAOTF will provide CDC with the same sort of identifying, service, and absence information as it provides for those individuals included in the 2 other cohorts.

Vietnam Experience Study

The procedures for selecting individuals for the Vietnam Experience study will be substantially different from those used for the Agent Orange study -- the process will start with the selection of individual personnel files in the National Personnel Records Center in St. Louis rather than with the selection of military units. We understand that, for draftees and single term enlistees in the Army infantry, assignment to Vietnam or to some other part of the world was essentially a random process, but this was probably not the case for other services. Since it is desired to compare men who went to Vietnam with men who did not, but who had a more or less equal chance of being assigned to Vietnam, CDC will limit this study to Army veterans in the non-officer ranks.

The St. Louis records center houses personnel files for all discharged service persons, except the living retired and those who are in the active reserves. Soon after discharge, the military personnel folder is transmitted to the center where it is identified by service and given an accession number. Since a master list by service and accession number is available it is possible to select a sample of individuals from the records center stacks. Unfortunately, the master accession list does not indicate whether the discharged soldier served in Vietnam or not, nor his rank, nor any other vital information. Thus it will be necessary to pull the records of each individual identified from the accession list to determine if he qualifies for inclusion in the study. Those individuals found to be ineligible will be replaced with another serviceman according to strict criteria. This eligibility assessment will be done at the records center, and coordinated by AAOTF staff; records of individuals found to be eligible at this preliminary review will be sent to AAOTF headquarters in Washington, D.C. for complete review. CDC and AAOTF staff visited the St. Louis Records Center and reviewed a random sample of 1259 military records. Of this sample, 563 records were of veterans who met the preliminary study criteria for inclusion. Of those qualified, 43% had served in Vietnam, 21% in Germany, 7% in Korea, and almost all of the remaining 29% served only in the United States. The distribution by location of service and time of that service correspondends to Department of Defense data. This work indicates that the approach can yield a sample with relatively little wasted effort and CDC feels that it is far preferable to a sampling scheme based on a preliminary selection of military units.

The members of both cohorts for the Vietnam Experience study will be chosen from among soldiers with appropriate periods of active service. For the Vietnam service cohort this should provide a year-of-tour distribution which is proportional to the year by year Army troop strength in Vietnam over the period 1966-1971. The selection procedure for the control cohort will be

such that its period of service distribution is equivalent to the Vietnam cohort. The cohort of men included in the Vietnam service cohort will have served only in the U.S. and Vietnam. It is proposed that the control or non-Vietnam cohort be chosen so that it comprises 3 groups: a group of men who served only in the continental US, a group whose members served in the U.S. and Europe and a group of those who served in the U.S. and Korea. This approach may allow an assessment of the effects of the experience of a foreign service, with the contrast between European and Korean service providing a contrast in the level of foreign environment of the duty stations. AAOTF will give CDC the same sort of information about each soldier in this study as will be provided for those men included in the Agent Orange study, except that no daily geographical location information will be given.

Data collection will be identical in the Agent Orange and Vietnam Experience studies; it will entail telephone interview of each locatable member of each study sample. (Attachment 5, AO/VE Questionnaire). Interviews will be performed by a competitively selected contractor who will be responsible for developing all supplementary forms, letters, etc. and for generating whatever additional locating information is necessary to complete the required interviews.

CDC will provide the contractor with a monthly list of approximately 1400 potential participants; government supplied information on each subject will include: name, date of birth, SSAN, last known address, and the name(s) and address(es) of next of kin (extracted from military records). The contractor will be required to verify the addresses provided or develop new ones and to determine the subjects' telephone numbers. Initial contact with each subject will be by letter, and the contractor will be required to exhaust all locator systems before contacting next of kin to establish subjects' whereabouts.

CDC tested the "locatability" of veterans of battalions using the IRS record system and telephone directory assistance. The Army Agent Orange Task Force identified 840 veterans, and IRS records match was made on 754 (89.8%) of them. Directory assistance verified address and provided a telephone number for 360 (47.9%) of those individuals; verified address, but provided no telephone number (unlisted)for 106 (14.1%) more. Directory assistance was unable to match name and address for 286 (38.0%) subjects; however, in 36 of these "no match" cases the operator indicated that there was a listing for the name at a different address; so the chances of locating those individuals should be quite good. Based on this experience, the contractor can reasonably expect to be able to locate approximately 67% of the subjects provided simply by using government provided information and by contacting directory assistance.

The first mailing to a potential respondent will identify the study and explain its purpose; it will also contain a toll free (800) number which a potential respondent can call for additional information. (Attachment 6, Initial Contact Letter--Draft). The contractor will be responsible for developing the final contact letter. This mailing will indicate the voluntary nature of participation and will also inform the subject that he will be contacted by telephone for an interview.

First telephone contact will be made by an interviewer who will explain the purpose and procedures of the study, its voluntary nature, and attempt to elicit agreement to participate (Attachment 7, Draft text, initial telephone contact). If the subject is willing to proceed, the interviewer will administer the questionnaire. If a practical method for doing so can be devised, the interviewer will be blinded to the cohort status of the respondent.

Subjects who do not respond to the initial mailing or to whom the first letter is undeliverable will be included in a locating system which involves at a minimum, telephone company sources, credit bureau, post office forwarding, and DMV (driver's license). The contractors final locating effort will be to contact the subjects' recorded next(s) of kin. Contact with next of kin would be by mail with possible telephone follow-up.

Subjects who initially decline to participate will be contacted three times before being finally classified as refusals. Two attempts to motivate participation will be made by telephone and a final effort in person. If the field worker is unsuccessful in eliciting cooperation, he will attempt to ascertain the subjects' reasons for non-participation and terminate the contact. At no time will study representatives use coercive methods to secure subject cooperation.

Selected Cancers Study

As noted before, this part of CDC's efforts to address concerns of Vietnam veterans will take the form of a population-based case-control study. A case-control study will be conducted because a cohort study would require truly massive sample sizes to detect an increased risk for such rare diseases, much larger samples than those proposed for the Agent Orange and Vietnam Experience studies. Studying such large samples would unnecessarily delay CDC's ability to provide answers to veterans about their risks for more common disorders.

The term population-based implies that all cases of sarcoma, lymphoma, nasopharyngeal, and liver cancer in defined population groups will be ascertained and an attempt made to include them in the study. This will confer at least two major advantages over studies done with cases collected by other methods: 1) since all cases arising in a population are ascertained, the concerns about biases of ascertainment which always attend other case selection strategies are not at issue, and, 2) a population-based study allows estimates of attributable risk, not just relative risk. The control group will be chosen from the same population as is the case group, and this will allow estimation of disease incidence rates by veteran status.

It is proposed to use the Surveillance, Epidemiology and End Results (SEER) Centers, which are sponsored by the National Cancer Institute, as the source of cases. The SEER Centers ascertain nearly all people newly diagnosed with cancer in at least 10 defined population areas (National Cancer Institute, 1981). These areas are: the states of Connecticut, Hawaii, Iowa, New Mexico, Utah, and the Commonwealth of Puerto Rico; and the metropolitan areas of Atlanta, Detroit, San Francisco, and Seattle. All of the SEER Centers contacted by CDC have indicated that they are interested in participating. Overall, interest in participation appears high because the SEER centers want to continue to build and demonstrate their epidemiologic potential. In addition, the centers each employ at least one epidemiologist, many of whom have been involved with the issue of cancer and chemical exposures and who view the proposed study as personally interesting. Overall, CDC believes that the SEER network is a superb epidemiologic resource that has been proven in other large case-control studies such as those which investigated the association of bladder cancer with artificial sweetener use (Hoover et al., 1981) and uterine, ovarian, and breast cancer with oral contraceptive use (Layde et al., 1983). Other population-based cancer registries may be utilized for case ascertainment if they are interested in collaborating in this study and if their case ascertainment is complete and rapid enough.

All cases of soft tissue sarcoma, lymphoma, nasopharyngeal and liver cancer occurring from July 1, 1984, to June 30, 1988, in males with birthdates 1929-1953 who reside in the geographic areas covered by the participating population-based cancer registries will be included in this study; the cases will be contacted and interviewed within 3 months of diagnosis. This age group has been selected because it includes the men most likely to have served in Vietnam between 1965 and 1971. Since soft tissue sarcomas are so rare, CDC has considered including additional cases diagnosed prior to July 1, 1984, in order to increase the power of the study to detect an association which may be present between herbicides and/or service in Vietnam and sarcomas. This possibility has been (tentatively) rejected for two reasons: 1) most importantly, the Swedish studies which suggest a relationship between sarcomas and occupational exposure to 2,4,5-T indicate a mean latency period between first exposure and diagnosis of about 16 years. Therefore, including cases which arose prior to 1984 might give only an illusion of increased power; 2) because the fatality rate for soft tissue sarcoma is quite high (Tucker et al., 1982), information about early cases and controls would frequently have to be gathered from next-of-kin instead of the affected man. However, this latter point would not be a major concern if data collection for these cases was limited to relatively simple items, such as whether the man served in Vietnam.

Four histologic review panels each composed of 2-3 pathologists will be established--one group to review each type of cancer. The groups will receive a set of slides or tissue block on each case and will establish their own diagnosis without knowledge of the presumed diagnosis. Interviews with cases will not be delayed for confirmation by the pathologic review panels.

The selection of controls will be by the method of random digit dialing (RDD). Telephone numbers are randomly phoned and a brief census of the household is made. If a man of the right age is found, then he will be asked to participate in the study. This method worked successfully in the National Cancer Institute Bladder Cancer study (Hoover et al., 1981) and CDC's Cancer and Steroid Hormone Studies (Layde et al., 1983). Over 90% of households that had eligible women in CDC's study yielded an interview; the NCI results were similar. Unlike the usual methods of collecting a sample of a population, which depend on making at least a partial in-person census of the geographic area, RDD allows this to be done by telephone, which clearly is less expensive and far more practical. About 95% of households have telephones. In addition, several researchers have documented how well samples chosen by RDD reflect the general population. The main concern is that people of very low socio-economic status may be underrepresented in the control group. CDC feels the effect of this potential bias will be small for 2 reasons: 1) our control group will be so large that some very poor people will be included; 2) an analysis stratified by socio-economic status should help ameliorate whatever bias is present. Based on the age and race distributions of cases, CDC will select controls from the list of eligible men such that the overall age and race distribution of the controls will be similar to that of the cases. As the study progresses, if the age distribution of cases is different from expected, control selection can be modified.

Data collection for the Selected Cancers Study will differ from that in the cohort studies previously described in that a different questionnaire will be used and it will not be practical to employ a computer assisted telephone interview due to the relatively small number of subjects available for interview at any one time.

The SEER Centers which identify the cases of interest will also perform the interviews (Attachment 8, SCS Questionnaire). CDC will select controls by means of a random digit dialing process. Potential controls will be informed by telephone of the purpose of the study and its voluntary nature; they will then be asked if they would be willing to participate in a telephone interview if selected. Those individuals who agree will be asked for age and race information (for matching purposes) and included in the pool of potential controls.

Contact and interview procedures will be the same for both cases and controls. The participating SEER Centers will send a letter explaining the study and its voluntary nature to each case/control (documents to be developed by contractors). Three days after the initial mailing an interviewer will make a follow-up telephone call to answer questions and make an appointment to complete the telephone interview; ideally, the interview will not be aware of the case/control status of the subject.

Experience in similar studies suggests that participation rates will be relatively high (ca 90% of cases; at least 75% of controls); thus no elaborate motivating procedure has been established. Both subjects and controls who are undecided or who initially refuse interview will be called a second time by an interview supervisor who will attempt to secure participation or, at least, ascertain the reason(s) for refusal.

Sample Sizes, Statistical Power and Participation Rates

Agent Orange and Vietnam Experience Studies

3. Response Rates and Power

The sensitivity (power) of these studies to detect a real increased risk among the veterans in any one of the cohorts depends on several factors, most prominently the numbers in each of the cohorts, the prevalence or incidence of the condition of concern, the amount of misclassification on the variables used to define the cohorts, and the magnitude of the increased risk.

It is proposed that each of the cohorts included in the mortality follow-up and health interview phases of these studies be composed of 6000 men. The number 6000 was chosen since this will give good power (beta=alpha=0.05, 1 tail) to detect a 2-fold increase in the risk for health outcomes normally occurring at the rate of about 5 per 1000 in comparisons of two cohorts (if there is little or no misclassification in the selection of men for the cohorts). A high beta level, equal to the alpha level, is suggested since CDC believes that as much attention should be given in these studies to type II errors as to type I errors. CDC further recommends that a sample of 2000 be selected from each of the cohorts for the medical, psychological and laboratory phase of the studies. This number is suggested since it will provide good power (beta=alpha=0.05, 1 tail) to detect 2-fold increases in the relative risk for health outcomes which ordinarily occur at the rate of 1.5-2.0%.

A major limitation of the sample size calculations for the cohort studies is that no good data exist on the expected prevalences of the outcomes postulated to be associated with TCDD exposure in populations similar to the veterans being studied. The occurrence of many of these conditions has never been assessed in population-based surveys. For some conditions there are data for men of the relevant ages from NCHS's Health Interview Survey (HIS) and Health and Nutrition Examination Survey (HANES). However, these national surveys may not accurately estimate the rate of chronic diseases in veterans -- men who had to pass fairly rigorous medical examinations to get into the Army. In a sense, we will not be certain of the actual statistical power to detect increases in specific diseases until the analysis is underway and we know the frequency of the specific diseases in the unexposed cohorts.

Perhaps this discussion begs the question: How were the sample sizes for each cohort of 6,000 for mortality assessment and interview and 2,000 for examination and laboratory testing chosen? Because of the paucity of relevant prevalence data these choices were necessarily somewhat arbitrary, however, CDC believes they are appropriate to detect an increased risk of important health outcomes in exposed veterans. For example, the cumulative total cancer incidence in the "unexposed" groups of veterans from 1968 to the time of the interviews is expected to be about 6 per 1,000 based on data from the Surveillance, Epidemiology, and End Results (SEER) network of the National Cancer Institute. Therefore, we will be able to detect a 2-fold increased risk for this critical outcome (and all outcomes that occur in more than 5 per 1,000 of the unexposed). For the examination and laboratory testing phases we should be able to detect 2-fold increased risks of abnormal outcomes for dichotomous variables that occur in more than 1.5% - 2.0% of the unexposed. Based on HIS and HANES, these should include such important conditions as ischemic heart disease and diabetes mellitus. For continuous outcome variables, such as the results of most laboratory tests, we should be able to detect even modest differences between the exposed and unexposed groups.

The power calculations have been made on the assumption that categorical data analysis will be done on the basis of a single 2x2 table for each disease. It is very unlikely that the situation will be simple enough to allow such straightforward analysis. Rather, it is anticipated that analysis will involve multiple variables and this may reduce power, if unnecesary variables are inadvertently included. Although the reduction should not be great, the situation is far too complex to allow any a priori estimation of just how large it may be. Another factor which may reduce power is misclassification of the variables used to define the cohorts ("exposure" variables) -- if the misclassification is random. Of particular concern is the possibility that the records which have to be used to define the first two Agent Orange study cohorts ("likely exposed" and "likely not exposed") are so incomplete and/or inaccurate that there will be a sizeable amount of random misclassification in respect to true herbicide exposure. If this is the case then power will be reduced, possibly to a significant degree, and the measures of effect will be biased toward the null. If misclassification in respect of exposure is present and not random, power would also be affected and the measures of effect could be biased toward or away from the null.

In order to achieve the power desired in the interview phase it will be necessary to begin with cohorts which are larger than 6000 because some of the desired study participants will not be located and some, once located, will decline to participate. CDC recommends that the goal for this phase should be a location rate of 85% and a 85% interview rate among those located, for an overall participation rate of 72%. Therefore, CDC recommends that the AAOTF select 8350 (approximately 6000/0.72) veterans for each of the cohorts.

If the interview phase is successful, it should not be difficult to obtain the cooperation of 2000 men per cohort for the examination phase. However, there is considerable concern that we may have difficulty in achieving a high rate of participation among those who are selected for inclusion in this phase. In other words, our concern here is not that we will be unable to reach the desired sample size of 2000 per cohort but rather that participation is not limited to a highly selected group of men. It is felt that the best we can hope for is a rate of 60% cooperation (i.e., 83% of the subsample composed of those who are located and agree to be interviewed [0.83=0.60/0.72]). This may be an optimistic goal. The Ranch Hand study team had an examination phase participation of 87% among the Ranch Handers and 76% among the controls. CDC feels that the Air Force success can only be a goal which we can hope to

emulate but not necessarily achieve. The NCHS experience of about 70% participation in its Health and Nutrition Examination Surveys can also be considered (the interview survey cooperation was about 95%). CDC feels that inferring directly from this experience to its own situation probably gives a somewhat optimistic expectation. The NCHS examinations were done in trailers which were located within easy commuting distance of the study participants, whereas most of CDC's study subjects will have to be transported to the examination sites by air. Moreover, the NCHS sample included persons of both sexes and all ages while CDCs cohorts will be composed wholly of men of a narrow age range, a group which will probably have a lower than average propensity to participate.

It will be desirable to assess study participants and non-participants with respect to differences in health and differences in exposures to health-influencing factors. Some assessment of this sort will be possible for the examination phase--men who are interviewed and who are invited but decline to participate in the exams will be compared to men who are examined. This comparison will make use of data gathered in the interviews. Unfortunately, a similar type of comparison cannot be made for those who are interviewed and those who are not. CDC will have very little, if any, health related information about men who will not participate or who are not located. If feasible, comparisons will be made between interview respondents who readily participate and those who agree to be interviewed only after considerable coaxing. Similar comparisons could be made between veterans who are easy to locate and those traced only with considerable difficulty. While not ideal, such comparisons may provide insights into the characteristics of those refusing to participate and those not located.

Selected Cancers Study

As with the cohort studies, the power of this study to detect a real increased risk among Vietnam veterans depends on several factors, in this instance the number of cases and controls interviewed, the proportion of controls who served in Vietnam (and/or the proportion exposed to herbicides), the amount of exposure misclassification (misclassification of disease should be held to a minimum through the use of panels of pathologists, and the magnitude of the increased risk. The Veterans Administration estimates that 2.9 million veterans served in Vietnam. As of July 1, 1983, the United States civilian male population aged 30-55 was estimated to be 34,253,000. Therefore, it is estimated that 10 to 15% of males in the age group of Vietnam veterans (birthdates 1929-1953) actually served in Vietnam. Power figures for this study are presented in Table VI. We have decided to study about 1,300 controls since this number will give fairly good sensitivity for a 2-fold increase in risk, and adding further numbers to the control sample will do little in terms of improving the power. It is unlikely that small real increases in risk can be demonstrated. Moreover, if Agent Orange or some other factor really has increased the risk of exposed veterans a small amount, and if only a small porportion of veterans were exposed to a toxic dose, the sensitivity of this study will be much lower than the figures presented. It should be noted that this will be a large case-control study, based on all soft tissue sarcoma, lymphoma, nasopharyngeal, and liver cancer cases which have occurred in a population of about 2,481,000 males aged 30-55 over a period of 4 years. Viewed from a somewhat different perspective, it will have roughly the same sensitivity as a cohort study which assembled about 10% of all Vietnam veterans (290,000) and the same number of non-veterans and assessed the occurrence of soft tissue sarcomas over a period of 6 years and lymphomas over a period of 3 years. The cost of such a study would far exceed the cost of the proposed study.

Table VI
Power[1] of Selected Cancers Case-Control Study
to Detect Increased Relative Risks

a) 2-fold Increase in Relative Risk for Vietnam Veterans in General

Study Year 1

Type of Participant	Number[2]	Control Group Prevalence of Vietnam Veterans 0.050	0.075	0.100
Soft Tissue Sarcoma	106	0.45	0.57	0.66
Lymphoma	331	0.67	0.82	0.90
Nasal & Nasopharyngeal	42	0.30	0.37	0.43
Liver	42	0.30	0.37	0.43
Controls	325			

Study Year 2

	Number[2]	Control Group Prevalence of Vietnam Veterans 0.050	0.075	0.100
Soft Tissue Sarcoma	212	0.70	0.83	0.90
Lymphoma	662	0.92	0.98	0.99+
Nasal & Nasopharyngeal	85	0.47	0.58	0.66
Liver	85	0.47	0.58	0.66
Controls	650			

Study Year 4

	Number[2]	Control Group Prevalence of Vietnam Veterans 0.050	0.075	0.100
Soft Tissue Sarcoma	319	0.84	0.94	0.97
Lymphoma	993	0.98	0.99+	0.99+
Nasal & Nasopharyngeal	128	0.60	0.73	0.81
Liver	128	0.60	0.73	0.81
Controls	975			

Study Year 4

	Number[2]	Control Group Prevalence of Vietnam Veterans 0.050	0.075	0.100
Soft Tissue Sarcoma	425	0.92	0.98	0.99+
Lymphoma	1324	0.99+	0.99+	0.99+
Nasal & Nasopharyngeal	170	0.70	0.82	0.89
Liver	170	0.70	0.82	0.89
Controls	1300			

Table VI (continued)

b) 2-fold and 5-fold Increases in Relative Risk Under Assumption of 7.5% Control Group Prevalence of Vietnam Service and 3 levels of Possible Agent Orange Exposure Among Vietnam Veterans (Study Year 4 only)

2-fold Increase in Relative Risk For Agent Orange Exposed Vietnam Veterans

Type of Participant	Number[2]	Possible Prevalence of Agent Orange Exposure Among Vietnam Veterans 0.10	0.25	0.50
Soft Tissue Sarcoma	425	0.33	0.62	0.85
Lymphoma	1324	0.49	0.85	0.99
Nasal & Nasopharyngeal	170	0.23	0.41	0.61
Liver	170	0.23	0.41	0.61
Controls	1300			

5-fold Increase in Relative Risk for Agent Orange Exposed Vietnam Veterans

Type of Participant	Number[2]	Possible Prevalence of Agent Orange Exposure Among Vietnam Veterans 0.10	0.25	0.50
Soft Tissue Sarcoma	425	0.96	0.99+	0.99+
Lymphoma	1324	0.99+	0.99+	0.99+
Nasal & Nasopharyngeal	170	0.81	0.98	0.99+
Liver	170	0.81	0.98	0.99+
Controls	1300			

1 Power calculations with 1-tail, alpha = 0.05 by method of Casagrande JT, Pike MC: An improved approximate formula for calculating sample sizes for comparing two binomial distributions. Biometrics 1978;34:483-6.

2 Estimated number of parcicipants

4. Pretests and Pilot Studies

Agent Orange and Vietnam Experience Studies

Two major categories of procedures need to be assessed before the main studies begin. First, there are a number of issues involving the manipulation of military records which need more work. Second, there is the matter of locating study subjects, securing their cooperation, and assessing the various study instruments (questionnaires, examination and laboratory protocols). The failure of any of the proposed procedures in preliminary tests will require revision of the procedures, and, if major failures are identified, outside consultation and peer review of new proposals.

All proposed study procedures will be tested in a series of interrelated pilot studies and pretests. For the purpose of the discussion here, the term "pilot" study will be reserved to refer to the final process of assessing participation rates and evaluation of interview and examination instruments just before the start of the main cohort studies. The term "pretest" will be used to refer to evaluations of all other procedures. It might be desirable to do formal and complete pilot studies for each of the three proposed studies. However, because such an approach would unnecessarily lengthen the time required to complete the two cohort studies, CDC recommends that procedures be tested with a series of related "pretests" and "pilot" studies. In those situations where one among several alternative procedures clearly seems to be the method of choice, only that method will be pretested and the other alternatives tried only if the preferred choice fails. In other instances, there may be no clear preference and then more than one procedure will be pretested.

The general approach for the pretests will be early and close monitoring of circumscribed aspects of the study procedures. Several pretests of procedures which would be sequentially applied in the main studies can be done simultaneously. It is obvious that much time could be saved by using this approach. On the other hand, if problems are identified there would be minimum delay and relatively little work necessary to repeat the process using corrected procedures. Moreover, if no major problems are identified then the data generated during the pretest could be used for the next pretest step or, for some procedures, the processes judged to be successful in pretests could be used straight away for the main studies.

An example of the pretest approach is the evaluation which was done to assess the locatability of male veterans, and the plans for making the same sort of evaluation for female veterans. The AAOTF transmitted to CDC identifying information for some 840 male veterans and CDC sent the information to the IRS to begin the locating process. The veterans used for this pretest were chosen because they were attached to two units that the AAOTF had worked with previously (1st of the 9th and the 31st Engineers). The AAOTF had the names of the individuals who served in these units in 1967-1968 at hand, and only needed to request the personnel records from the St. Louis records center in order to obtain such items as SSNs and names and addresses of relatives. IRS was able to provide locating information for 754 (89.8%) of the 840 veterans identified for CDC by the AAOTF, and of the 754 CDC was able to confirm locating by contact with directory assistance for 502 (66.6%) of the individuals. Thus, it appears that approximately 60% of subjects will be locatable through initial record check and the telephone system; contact of the remaining 40% will require additional system checks (e.g. SSA) including vital status determination. Clearly, "field follow-up" will be necessary to contact some of the subjects, and a subset, the size of which is currently unknown, will be unlocatable. The types of additional systems checks, extent of field work necessary, and the probable size of the unlocatable group will be determined during the pilot study.

The pilot study would be an integrated test of the contractor's locating systems, interview procedures, and the questionnaire itself. The pilot will involve approximately 550 veterans and require three months to complete. Results of the pilot would be reviewed continually, and changes in procedures and in the instrument could be incorporated as the need was discovered. Thus, at the end of the pilot period, data collection could begin immediately in the main study cohorts. Therefore, this request for data collection approval is for both the pilot and main studies. All changes in the questionnaires and collection procedures would be forwarded for review before main study data collection began.

Military Records Pretests

Because AAOTF has had extensive experience in working with records from the Vietnam era it is not expected that major problems will be discovered in the area of records manipulation. Even so, a more comprehensive test of the proposal to derive a sample of men for the Vietnam Experience study from the St. Louis records center was conducted to evaluate any problems which might arise in attempting to make the non-Vietnam veteran cohort match the Vietnam cohort in regard to calendar years of service. To this end a pretest sample of 241 Vietnam veterans and 322 non-Vietnam veterans was chosen. No serious problems were identified with the procedures. The samples of veterans gathered during the pretest can be used as a part of the pilot study.

Much work needs to be done with the records which will be used to classify exposure. While abstracting such data as daily unit locations is apparently simple, at least for those familiar with the records, so little actual work in this regard has been done for the purpose of assessing herbicide exposure it must be considered a relatively untried process. Rather than incorporate this phase into a formal pilot study, it is proposed that the process be evaluated by constant monitoring during the preliminary unit selection process when the locations of the 50 battalions are identified. Even less experience has been accrued in the process of checking troop locations against the herbicide records. In particular, the schemes proposed in this protocol for scoring herbicide encounters have not been tried and their usefulness is unknown. Two pretests of these schemes will be made. The first pretest will take place when the randomly selected units from III Corps are evaluated for the purpose of ranking them on the herbicide encounter scores; if there appear to be no problems at this stage, then CDC will have the AAOTF immediately proceed to the next step of the study, which will be the choice of individuals for the main studies. Later the encounter scoring scheme will be tested again for individuals.

Location Rate, Participation Rate and Instrument Assessments

As mentioned above, some parts of the evaluation of the locatability of the cohort study subjects are now underway. This will continue as a part of the pilot study. Besides providing more information about locatability, the cohort pilot study will give information about expected main study participation rates and about possible difficulties with the interview instrument and examination protocol. The pilot study will be nearly a main study in miniature, the major exception being that the proposed selection process for the Agent Orange study cohorts will not be used to choose any of the pilot study subjects. As mentioned above, the subject selection process for the Vietnam Experience study provided 563 veterans eligible for the pilot study. Rather than wait for the process of ranking the companies in the 50 battalions from III Corps to be completed before selecting a pilot sample for

the Agent Orange study, CDC recommends another approach to save time. It is proposed to simulate the Agent Orange main study through the use of 400 veterans who will be chosen from among the 110-120 combat battalions which were stationed in III Corps during 1967-1968.

The selection of these pilot study veterans will involve the initial random selection of 10 companies from the 110-120 battalions. From each of these companies, 40 randomly chosen men will be selected. Although the cohort pilot study will simulate the main studies, the results will be considered in two stages -- an interview stage, which will almost certainly be completed first, and an examination stage. If the interview stage proves to be successful, CDC will proceed with the interviews for the full study samples even though the results of the examination stage may not be available.

As noted elsewhere, CDC is concerned that it may be difficult to reach an acceptable level of participation in the examination phases of the studies. The Ranch Hand study group's enviable success in this regard is attributed in large measure to their treatment of their study subjects as "VIPs." CDC will attempt to duplicate this treatment. Since there may be monetary factors which influence participation in the examination phase, CDC will test the effect of recompensing the subjects for lost time; offering recompense may help to raise paticipation or it may decrease it if the offer offends a sense of altruism. In addition, the effect of travel to distant locations for the examinations may enhance or deter participation. If it appears that more than one examining center will need to be used in the main studies, a test of the effect of distance to the center will be made in the pilot studies.

Selected Cancers Study

The Selected Cancers Case-Control Study procedures will be field tested in 2-3 SEER centers using fewer than 9 cases of lymphoma. Only lymphoma cases will be used because of the rarity of the other "selected" cancers and CDC cannot risk "wasting" them on a pilot study. Only 2-3 SEER centers will be used to minimize the time required -- CDC feels that more are not required because of its previous success with the Cancer and Steroid Hormone study. The main purpose of a pilot study will be to evaluate the participation rate of males aged 30-49 and the interview instrument. The work done by the AAOTF on scoring herbicide exposure likelihood for CDC's birth defects study is considered a valid surrogate for an assessment which could be done specifically for this study.

5. Statistical Design

The statistical aspects of these studies were dealt with by J. David Erickson, D.D.S., M.P.H., Ph.D.; Peter M. Layde, M.D., M.Sc.; and Matthew M. Zack, M.D., M.P.H. These individuals are all affiliated with CDC's Chronic Diseases Division and may be reached at (FTS) 236-4072.

The identity of the data collection agencies is unknown at this time, since it is planned to contract for these services, and the competitive process is not complete. Data analysis will be performed by Center for Disease Control staff under the direction of J. David Erickson; Dr. Erickson may be reached at (FTS) 236-4068.

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