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**PROTOCOL FOR EPIDEMIOLOGIC STUDIES OF
THE HEALTH OF VIETNAM VETERANS**

1. Cohort Study of the Long-Term Health Effects of Exposure to Agent Orange in Vietnam.
2. Cohort Study of the Long-Term Health Effects of Military Service in Vietnam.

and

3. Case-Control Study to Determine the Risks for Selected Cancers Among Vietnam Veterans.

to be conducted by

CENTERS FOR DISEASE CONTROL

PUBLIC HEALTH SERVICE

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Protocol for Epidemiologic Study of the Health of Vietnam Veterans

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1. Introduction

In response to the concerns of Vietnam veterans regarding their health, the Centers for Disease Control (CDC) herein proposes three distinct but related studies which are in addition to CDC's ongoing birth defects study. CDC believes that they provide the best opportunity to answer questions of importance to Vietnam veterans and their families, even though some aspects of the proposed studies are not scientifically ideal. The concerns of the nearly 3 million men who served in Vietnam for their health are real. If Vietnam veterans are at an increased risk of ill health, the personal and public health impact cannot be overestimated. In any case, the concerns and uncertainty alone represent a significant problem. CDC will be pleased to be able to provide a service to the nation's Vietnam veterans by conducting these studies to evaluate their health.

In this document CDC proposes two historical or retrospective cohort studies and one case-control study. One of the cohort studies will compare the health of a group of male U.S. Army veterans of the Vietnam conflict with the health of a group of male Army Vietnam-era veterans who did not serve in Vietnam. The purpose of this study will be to make an assessment of the possible health effects of the general Vietnam service experience, and will hereafter be referred to as the "Vietnam Experience" study. The other cohort study, which is designed to evaluate the health effects of possible exposure to herbicides (primarily Agent Orange), will compare the health of three groups or cohorts of male Vietnam veterans who differ in their probable level of exposure to Agent Orange and other herbicides. This second cohort study, to be referred to as the "Agent Orange" study, will also be limited to veterans of the Army. The third study will be a case-control study to evaluate the risk of contracting soft tissue sarcoma and lymphoma among Vietnam veterans (and/or those exposed to herbicides); this study will be designated as the "Sarcoma/Lymphoma" study. It is a critical part of CDC's effort because there is a specific concern about veterans' risk for these cancers, and the cohort studies are not large enough to provide answers about them. Cases and controls for the Sarcoma/Lymphoma study will be limited to males who were of draftable age during the Vietnam conflict, and will include veterans from all branches of the military.

Each of the two cohort studies will have three major components: 1) a mortality assessment (mortality follow-up will be repeated every 5 years for the foreseeable future); 2) a health interview; and 3) a clinical and laboratory assessment. The studies will have several other features in common. However, the sampling plans will differ and some of the health outcomes measured in the interviews and clinical assessments will receive different emphases in the two studies. The Sarcoma/Lymphoma case-control study will involve a health and exposure interview.

Taken together, the three studies proposed in these protocols, along with CDC's ongoing birth defects study, represent a fairly comprehensive approach to the health concerns of Vietnam veterans. In many respects, the studies are complementary to one another. Without conducting each of the three studies proposed herein, the CDC does not believe it can adequately assess the concerns of Vietnam veterans.

This set of protocols presents the general framework of CDC's proposed studies. The studies will be very large and complex undertakings and not all details are presented; indeed, many details cannot be presented until work proposed in the protocols is done. CDC's policy of openness about its plans will continue as the studies progress.

Historical Note on CDC's Involvement

Public Law 96-151 requires that the Veterans Administration (VA) conduct an "epidemiological" study of U.S. veterans to assess the possible health effects of exposure to herbicides and dioxin during the Vietnam conflict. Public Law 97-72 expands this mandate to include the study of other environmental exposures which may have occurred in Vietnam. At about the time Public Law 96-151 was enacted, CDC proposed its ongoing birth defects study to assess the Vietnam veteran's risk of fathering children with congenital malformations.

The responsibility for the design, conduct, and analysis of studies responsive to these laws was transferred, by an Interagency Agreement, from the VA to CDC in mid-January 1983. In November 1982 a team of CDC scientists prepared a "protocol outline" (Appendix A) which set down the rudiments of CDC's study plans, and the outline served as the basis for the Interagency Agreement. The present document expands on and supplements the ideas contained in the November 1982 "protocol outline."

2. Background

The review of background information regarding the possible health effects of military service in Vietnam presented here is intentionally very brief. It is intended to give an appreciation of the rationale for CDC's proposed studies. Those who desire more detail on health effects are referred to Appendix B and this document's reference list; the comprehensive review of the literature which was conducted for the VA is a particularly good source of information on herbicides. Those familiar with the literature can proceed directly to Section 3.

2.1 Herbicide Usage in Vietnam

Herbicides were used for three principal purposes during the Vietnam war: defoliation - to cause trees and plants to lose their leaves in order to improve observation; crop destruction - to destroy the food value of certain crops; and, on a smaller scale, to clear vegetation around fire bases and other installations, around landing zones, and along lines of communication. The use of herbicides during the Vietnam war began in 1962, was greatly expanded during 1965-1966, and peaked from 1967-1969. In 1969 it was reported that mice exposed to certain herbicide components bore offspring with birth defects. Between 1970 and 1971 the use of herbicides was phased out in Vietnam.

The tactical military project for the aerial spraying of herbicides in South Vietnam was named "Operation Ranch Hand;" this program used fixed-wing aircraft and disseminated the bulk of the herbicides used in Vietnam. Smaller quantities of herbicides were applied from helicopters, trucks, riverboats, and by hand applicators. At least two groups of U.S. personnel appear to have been at risk for exposure to herbicides--those involved in the transport and dissemination of the agents and those exposed at the time of spraying, such as troops on the ground. Although exposures may have occurred during transportation (e.g., because of damage to containers), aircraft crew -- particularly flight mechanics and crew chiefs -- were thought to be at greatest risk. Even though the major portion of herbicides used was disseminated by Ranch Hand, a significant and even major source of exposure of ground troops may have been from non-Ranch Hand applications. Records of Ranch Hand missions are contained on the so-called "Herbs" computer tapes, and records of other herbicide applications are on the "Services Herbs" tapes (see Section 4.1.1).

Herbicides used for military purposes during the war were identified by color bands on their containers (e.g., orange, white, purple, etc.). The herbicide known as Agent Orange was most widely used in Vietnam. It was a 50:50 mixture by weight of the butyl esters of two phenoxy acid herbicides, 2,4-dichlorophenoxy acetic acid (2,4-D) and 2,4,5-trichlorophenoxy acetic acid (2,4,5-T). In addition, TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin, "dioxin") was a synthetic contaminant of 2,4,5-T; levels of TCDD contamination of Agent Orange ranged from 0.02 to 47 ppm, with a mean of about 2 ppm (Young et al., 1978).

2.2. Health Effects of Herbicides and Dioxin

The herbicide contaminant TCDD is considered to be one of the most toxic compounds known. Thus, any interpretation of abnormal findings related to 2,4,5-T exposure must take into consideration the presence of varying or undetermined amounts of TCDD. Single oral TCDD LD50's range from 0.6-2.0 ug/kg in the guinea pig to 1157-5051 ug/kg in the hamster (Schwetz et al., 1973; Olson et al., 1980; Kociba and Schwetz, 1982). A wide variety of health effects have been observed following administration of TCDD to experimental animals. Acute and chronic toxic effects in animals include carcinogenesis, maternally mediated teratogenesis, hepatic necrosis, decreased body weight, alopecia, chloracne, thymus atrophy, adrenal hemorrhage, immunosuppression (e.g., decreased cell-mediated immunity and lymphopenia), and other hematologic changes.

In humans, toxic effects have been reported after occupational exposure during the industrial synthesis of 2,4,5-trichlorophenol (TCP) and 2,4,5-T, after exposure in factories and in the surrounding environment following explosions which occurred during the synthesis of TCP, and after exposure to herbicides and other materials containing TCDD. Many of these studies had no, or inadequate, controls; exposure was usually of unknown magnitude and duration, to what were often mixtures of chemicals; and the total number of exposed persons was usually not reported. Available data on dermatologic, hepatic, neuropsychologic, immunologic, carcinogenic and reproductive effects are reviewed in Appendix B and briefly summarized below.

The most frequent and consistent acute health effect of TCDD exposure is chloracne, a refractory acne which is also caused by exposure to certain other halogenated hydrocarbons. Chloracne may be accompanied by hyperpigmentation and/or hirsutism and can persist for many years after exposure.

Porphyria, a liver disorder resulting in abnormalities of heme pigment metabolism and often accompanied by skin manifestations, has been reported after several industrial accidents. Other hepatic effects include structural alterations, changes in the biliary system and alterations in serum levels of certain liver enzymes.

Neurological and/or psychological effects have been reported after most episodes of accidental industrial exposures. Common complaints have included irritability, fatigue, weakness and pain, headaches, sexual dysfunction and loss of appetite. Signs of peripheral neuropathy, including decreased nerve conduction velocity have been reported.

Immunological effects have been observed in experimental animals, including changes in thymus and other lymphoid tissues. TCDD also suppresses immune function, particularly thymic-dependent function. Reduced mitogen responsiveness, and impaired skin-graft rejection and delayed hypersensitivity responses have been observed in animal species.

TCDD is carcinogenic in rats and mice; it appears to act as a tumor promoter in these species. Evidence is accumulating that human occupational exposures may be associated with an increased risk of soft tissue sarcoma and lymphoma. Somewhat weaker evidence suggests that herbicide exposure may be associated with nasal and nasopharyngeal cancers. Allegations that herbicide exposure is associated with primary liver cancer have emanated from Vietnam.

Reproductive effects in animals appear to be limited to maternal (fetal) exposures; the few studies that have addressed the possibility of paternally mediated effects have not shown differences in rates of poor reproductive outcomes between the exposed and non-exposed. The human data on reproductive outcomes after exposure is also generally negative, but most specific poor reproductive outcomes are rare, and the studies of men exposed in industrial settings have been relatively small.

2.3. Diseases Affecting U.S. Troops in Vietnam

Overall, the average annual hospital admission rates for diseases among soldiers in Vietnam (351 per 1,000 per year) were about 30% lower than for the China-Burma-India and Southwest Pacific theaters in World War II and 40% lower than for the Korean war. Malaria was the most significant medical problem in Vietnam, accounting for the greatest number of lost man-days. Diarrheal, skin, and venereal diseases were also significant problems. Before 1968 neuropsychiatric disorders were not unusually frequent among men serving in Vietnam, but by 1970 they became the second leading disease problem.

2.4. Current Health of Vietnam Veterans

Many Vietnam veterans believe that they may be at increased risk for a wide variety of diseases. Concerns voiced by Vietnam veterans include (to name just a few) dermatologic conditions, neurological disorders, reproductive problems, cancer, and infections. Unfortunately, little objective evidence is available regarding the health of Vietnam veterans relative to the health of other men of similar age. Indeed, this lack of data is a major reason for the studies proposed here.

Data are available, however, for certain health-related issues such as psychosocial adjustment. Psychosocial adjustment problems could, in one sense, be considered health outcomes and, in another sense, causes or effects of other health outcomes. The literature suggests that Vietnam veterans differ from other veterans and from non-veterans in the level of their educational achievement, occupational status, psychological symptoms (especially anxiety, depression, and anger), drug and alcohol use, and frequency of arrest.

2.5. Long-Term Health Status of Servicemen and Veterans

An additional literature review was done to provide background for the Vietnam Experience study. The most important finding of this review was not unexpected: because of medical selection at the time of induction into the military, ex-servicemen, especially officers, enjoy better long-term health than their counterparts who did not serve in the military.

It was thought that one would find many reports of studies that compared the health of men who had seen combat with the health of contemporary men who had not participated in combat. CDC was unable, despite an extensive search, to find such reports. The details of CDC's search and a review of some of the reports found can be found in Appendix B.

3. Study Design Overview

The purpose of this section is to provide a summary of the general rationale for CDC's recommendation for three separate studies; this will be useful background for the subsequent description of the proposed study procedures. The section reiterates and, in some respects, amplifies the "protocol outline" prepared by CDC in November 1982 (Appendix A).

3.1. Agent Orange Study

A good design for a historical cohort study of the possible health effects of herbicide exposure would involve the use of two groups of men who were as similar as possible except for their exposure to the herbicide. Ideally, one group would be free from all exposure, and the other would have been subjected to "meaningful" exposure. It appears that such an ideal is not attainable. Obstacles include 1) the fact that the military records that must be used to assess exposure were made during a war and are, therefore, of uneven quality; 2) the inability to define objectively "meaningful" exposure; 3) the difficulty in ensuring that veterans who were possibly or probably exposed (by whatever measure) are comparable (with respect to all things that might influence health) to veterans who were not exposed. These obstacles are formidable impediments to the accurate assessment of health effects of herbicide exposure. In view of these obstacles, CDC proposes what it considers the best (albeit imperfect) approach to studying this issue.

The important records that give information about troops are the company morning reports and the battalion journal files. The morning reports can be used to document the presence or absence of individual servicemen on a daily basis, and the daily journal files will indicate the locations of companies in time and space. The major herbicide records are those that document the time and location of fixed-wing aircraft applications of herbicide (Ranch Hand missions), base perimeter applications records, and information about Ranch Hand mission aborts. The choice of an individual for inclusion in the "exposed" cohort will be based on a measure of company proximity in time and space to herbicide applications, as documented by these records. Members of the "non-exposed" cohort will likewise be selected according to a measure of their company's distance in time and space from any herbicide applications. Because of the uncertainties involved in assessing exposure, the two cohorts will hereafter be denoted by the terms "likely exposed" and "likely not exposed," respectively.

The company records may contain gaps (i.e., whole periods of time missing) and are probably quite variable in terms of quality and detail, because they were created during the war. The herbicide usage records are known to contain errors with respect to the time and location of applications, and the degree of their completeness is unknown. They are far from ideal as the starting point for an historical cohort study. There may be opportunities to assess the accuracy and completeness of the herbicide usage records, and every effort will be made to pursue these opportunities (Section 4.1.1.). However, there are no possibilities for similar checking of the company troop records. Thus, the categorization of individuals with respect to their potential for herbicide exposure will be uncertain and will forever remain so.

The desire to ensure that troops classified as "likely exposed" to herbicides are comparable to "likely not exposed" troops with respect to other factors that might influence health also makes it difficult to design an "ideal" study. The underlying problem is that the use of herbicide was not equally distributed in Vietnam. Areas where it was heavily used were generally combat areas that differed in terrain and flora from areas where it was little used. These areas may also have differed in other important respects, such as indigenous diseases, level of combat intensity, and type of personnel deployed. It is for these reasons that CDC proposes choosing the "likely exposed" and "likely not exposed" cohorts from the same area of Vietnam. Unfortunately, because of the inherent limitations of the records, this approach may have the effect of increasing exposure misclassification (especially the categorization of those who were truly exposed into the "likely not exposed" group). These two competing forces, the desires for comparability and for maximum exposure separation, have drawn CDC to recommend a three-cohort design. Two of the three cohorts will be from the same area of Vietnam, III Corps (and the same time during the war, 1967-1968), but will differ in regard to their exposure likelihood. These two cohorts will be comparable but may suffer from imprecision of exposure separation. The third cohort will be drawn from other areas of Vietnam (but also from the same time period), areas where there is good evidence of little or no herbicide usage. This cohort will give maximum exposure separation from the "likely exposed" cohort but may suffer from a lack of comparability with respect to other health-influencing factors. This design is illustrated in the following 2 x 2 table which cross-classifies exposure by a measure of service experience.

		Likely Herbicide Exposure	
		Yes	No
A	Service Experience	Cohort 1	Cohort 2
B			Cohort 3

The empty cell, representing the combination of herbicide exposure with "Service Experience B," cannot be filled, because it is our understanding from the military that herbicide use was inextricably entwined with a certain service experience, as explained earlier in this paragraph. Because of the empty cell in the table, this design will present problems in analysis and interpretation. Moreover, the comparison of the first and third cohorts, which will ensure maximum exposure separation, may be subject to respondent bias; respondent bias should not be a problem in a comparison of cohorts 1 and 2, because individual respondents will probably be uncertain about their (study) exposure status. Despite these problems, we believe that this design is better than either of the other alternatives -- alternatives based on an approach that uses only two cohorts--either decreasing exposure misclassification by decreasing comparability or increasing exposure misclassification by increasing comparability. The results of the Ranch Hand study, soon to be released by the U.S. Air Force, may help in the interpretation of this design. The Ranch Hand study will compare the health of crew members who flew the herbicide spray missions with air crew members who did not fly spray missions. Thus, it will provide information about herbicide exposure in the absence of the general experience of ground troops.

3.2. Vietnam Experience Study

The idea of studying health effects which might derive from the "general experience" of having been in Vietnam is at once attractive and unappealing. In part, CDC recommends this study as a "backup" for the Agent Orange study -- if the Agent Orange study does not reveal any adverse health effects, veterans still will want to know if some other factors in their Vietnam service contributed to their perceived poor health. The major reason for CDC's recommendation is that there may have been many factors in addition to herbicide exposure which could have adversely affected those who served in Vietnam, in contrast to their counterparts who served elsewhere. It is also plausible that Vietnam veterans who did not see active combat in Vietnam were subjected to health-influencing events that were not part of the experience of those who served elsewhere. Any study which focuses on Agent Orange alone will obviously not test such a plausible multifactorial hypothesis. However, the multifactorial nature of this hypothesis makes the study of the "Vietnam experience" unappealing from the scientific point of view. The "experience" comprises numerous factors, many of which are unknown, poorly defined, or not quantifiable. Nevertheless, in our opinion, this is an important question to the Vietnam veteran and one that deserves as much attention as the issue of the possible effects of herbicide. Viewed in the broadest terms, the Vietnam "experience" could have influenced anyone who served there. A major concern about the validity of making a comparison of Vietnam and non-Vietnam veterans derives from an undocumented suspicion that there may have been preexisting differences between the two groups in terms of health-influencing factors and behaviors. If such differences existed and if they applied to all veterans, then a valid study of the Vietnam "experience" would not be possible. However, military personnel with whom we have consulted do not believe that such factors would have existed for all Vietnam veterans. Specifically, they believe that being sent to Vietnam was a matter of the "luck of the draw" (conditional on occupational specialty) for those who were in the Army and who were drafted or who were short-term enlistees. Serving in Vietnam, the U.S., in Europe, or elsewhere depended, in their opinion, on occupational specialty and the operational needs of the various commands. Thus, any given serviceman was at risk of serving anywhere there was a need for his occupational specialty. Individuals for the two cohorts of this study will be chosen on the basis of a review of randomly chosen personnel records located at the St. Louis records center.

3.3. Selected Cancers Case-Control Study

As noted in Appendix B, several Swedish case-control studies (Hardell and Sandstrom, 1979; Eriksson et al., 1981; Hardell et al., 1981) suggest that soft tissue sarcomas and lymphomas occur 5-6 times more frequently in workers occupationally exposed to TCDD-contaminated phenoxyherbicides than in those not exposed. In addition, a National Institute for Occupational Safety and Health review of four U.S. company studies seems to have demonstrated an excess of deaths from soft tissue sarcoma among workers employed in plants where chlorinated phenols and their derivatives were manufactured (Honchar and Halperin, 1981). These studies have generated a specific concern among Vietnam veterans that they may be at increased risk for sarcoma and lymphoma, but no published studies address this question. CDC's proposed case-control study will determine if men who served in Vietnam are at increased risk of developing these tumors. In response to suggestions received from reviewers

of CDC's draft protocol, individuals with primary liver cancer and nasal and nasopharyngeal cancers will also be included in the case group. These are quite rare cancers and, in the absence of the hypotheses regarding sarcomas and lymphomas, would probably not deserve special study. Thus, the major focus of this study will remain on sarcomas and lymphomas. "Cases" will be males in the age range of Vietnam veterans identified by population-based cancer registries as having the specified tumors. Because of the study design, other cancers could be easily added if an association with phenoxyherbicide exposure is suggested or if other evidence gives rise to specific concerns among Vietnam veterans.

In this study, information about other suspect risk factors for these cancers will be gathered. Thus, this study will permit an evaluation of their contribution to the occurrence of these cancers, both in Vietnam veterans and in males (in the same age range as Vietnam veterans) in the population at large.

4. Study Procedures

4.1. Selection of Study Subjects

The selection of study subjects for the two cohort studies will be based on a review of military records by the Army Agent Orange Task Force (AAOTF) according to criteria set forth below. Selection of subjects for the Agent Orange study will depend on a simultaneous consideration of the position of U.S. troops in Vietnam and the times and locations of herbicide applications as indicated by extant records; neither the location of troops nor their proximity to herbicide applications will play a part in the choice of subjects for the Vietnam Experience study. Choice of subjects for the Selected Cancers study will derive from work done by CDC and the cancer registries participating in the study. Since this study is a case-control study, beginning with persons with the cancers and those without, military records will not be used as a part of the selection process, although they will be used as an aid to assessing exposure to herbicide among subjects who turn out to be Vietnam veterans.

CDC intends to limit individuals included in all three proposed studies to men. The exclusive attention to males does not derive from a lack of concern about the health of those relatively few females who did serve in Vietnam. Rather, this decision is based on CDC's belief that if females are to be studied, they should be studied separately in sufficient numbers to allow meaningful conclusions to be reached about them as a group. Moreover, any study of women would require somewhat different sampling strategies and different emphases in interviews and medical examinations. CDC is concerned that a study of female veterans might be difficult to implement because of the probability that female veterans, once identified from military records, will be harder to locate than men because of the name changes which will have occurred because of marriages after discharge. The AAOTF and CDC are assessing the locatability of female Vietnam veterans. If this assessment proves that it is indeed possible to locate a sufficient proportion of them, CDC will design a separate study and prepare a protocol for review and possible funding. Such a study would probably most resemble the Vietnam Experience study proposed here for males, but a study of cancers similar to that proposed for males will not be possible -- too few women served in Vietnam for any meaningful case-control study to be done.

4.1.1. Agent Orange Study

CDC proposes to limit this study to draftees and single-term enlistees in the non-officer ranks who served in the Army (grades E1 through E5 only); 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 we believe 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 specialties, and pre-existing demographic factors easier. Inclusion of substantial numbers of draftees is also motivated by a desire to try to assess the possible association between volunteerism and health. (If, however, a large percentage of enlistees joined the Army because they felt that the draft was inevitable, such an assessment may not be possible.) 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 U.S. Army, has become most familiar with them, and is most confident about their quality. Moreover, the Air Force did not keep records that show the daily geographical placement of personnel, and rather limited numbers of Navy servicemen were stationed on land in the Vietnam theater. Even though all study participants will be males in the non-officer ranks who were in the Army, the results will probably be useful in making inferences about all men who had similar ground experiences and possible herbicide exposures in Vietnam; if there are no sex-specific effects, the same may be said about females.

As noted previously, three cohorts of men will be chosen for the Agent Orange study. The first two, 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 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 possibility of including soldiers who may have been exposed to herbicides, we will select the men included in these first two cohorts exclusively from combat battalions. Since these two cohorts will be chosen from an area where herbicides were extensively used, there is a potential for exposure misclassification. The third cohort will therefore be chosen from an area where there is good evidence that herbicides were not used. According to the AAOTF staff, this third cohort probably cannot be exclusively derived from combat battalions.

Veterans to be included in the first two Agent Orange study cohorts will be selected 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, indeed even a recommendation not to proceed with an Agent Orange study, may be required after pilot study assessments (see section 4.5.1.1. below). In summary, the steps required are:

- 1) select a geographical area and time of interest - this 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) choose 2 random subsamples of 25 battalions (125 companies) each from the 50 battalions chosen in step 3
- 5) abstract selected companies' locations for subsample 1 on all days in 1967-1968

- 6) using the "Herbs" and "Services Herbs" tapes, score the herbicide encounters of the 125 companies of subsample 1 on all days
- 7) rank the 125 companies of subsample 1 with respect to their cumulative herbicide encounters
- 8) 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
- 9) using the "Herbs" and "Services Herbs" records, score individual men chosen in step 8 for their herbicide encounters according to the scoring schemes used for battalions (step 6).
- 10) repeat steps 5 through 9 for the 25 battalions comprising subsample 2, with the following modification: rank herbicide encounters using the 125 companies of the 25 battalions of subsample 2 and the companies of subsample 1 which were not chosen in the first iteration of step 8

The rationale for these steps is presented below.

To limit the amount of records review required, we first restricted, on the advice of the AAOTF, the geographical area of consideration to III Corps and the time period to 1967-1968. This area and time period were selected because of a variety of factors, including the number of Ranch Hand missions and U.S. troop strength, which was near peak. The AAOTF has determined that about 110-120 Army combat battalions were stationed in III Corps at some point during that time (usual battalion strength was 1,000). The records of the companies attached to battalions determined to have served in III Corps will be the major source of information about troop locations.

The second step in the selection process will consist of a review of General Services Administration (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 believe 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, CDC proposes 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 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, more stringent criteria can perhaps 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 judged suitable during the second step. Step four will involve splitting the sample of 50 battalions into random halves of 25 battalions each. Fifty battalions will be sampled in order to limit the quantity of records review required, but this sampling should provide a reasonable estimation of the range of herbicide encounters (next paragraph). 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. 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. Step five will involve abstracting from company records (or battalion records, if necessary) all locations recorded for the selected companies on each day during 1967-1968.

The purpose of dividing the sample of 50 battalions into halves is to increase the speed with which CDC can proceed with the interviews and examinations. The AAOTF estimates that it will take 18 months to abstract location information for all 50 battalions and that it will take 12 months to do it for the first 25 battalions. Step five will involve abstracting from company records (or battalion records, if necessary) all locations recorded for the selected companies on each day during 1967-1968.

In step six, CDC will check the 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 Sciences 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 done at the time and that it look into the possibility of further accuracy checks. The "Services Herbs" tape primarily contains records of non-Ranch Hand herbicide applications (e.g., 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; other systems may be used if this seems warranted. 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. For each of the 3 exposure systems, the daily scores will then be summed over all days in 1967-1968 for each company.

Next, the 125 or so companies of subsample 1 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 "likely exposed" cohort and those at the bottom will contribute to the "likely not 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 (of both subsamples combined). If 55 companies each provide 150 suitable individuals, this number will allow some loss because of non-participation and will yield the number desired for each of the cohorts (see section 4.4.1.). About 40% of the final sample of men will be derived from subsample 1, and the remainder will be chosen after the re-ranking in the second iteration of steps 5 through 8.

The desire to omit the Marine Corps from this study can now be more easily understood. If Marines were 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 except 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 by the AAOTF from the National Personnel Records Center in St. Louis for soldiers considered eligible. The AAOTF staff 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 CDC can begin the process of locating the veterans and soliciting their participation in the studies. Later, in step 9, individual soldiers will be classified with respect to exposure to herbicides by a scheme similar to that noted above. At this step some men drawn from units at the upper end of the exposure scale may be found to have "low" individual exposure scores and vice versa. Such men might be assigned to the other cohort or they might be omitted from the study altogether.

The third cohort for the Agent Orange study will be selected by a different method. Areas in Vietnam where there would have been no reason for herbicide usage will be identified by the AAOTF and a roster of units which served in, 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. CDC will check the locations of these areas against the herbicide usage records to ensure that there was no herbicide use. Enough units will be randomly chosen from this roster for the required number of individuals to 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 that it provides for those individuals included in the two other cohorts.

4.1.2. 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 Army combat units, 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 the desire is 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 also proposes to limit this study to Army veterans in the non-officer ranks (grades E1 through E5).

The St. Louis records center houses personnel files for all discharged service persons, except the living retired and those 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, a sample of individuals can be selected from the records center stacks. Unfortunately, the master accession list does not indicate whether the discharged soldier served in Vietnam or not, his rank, or any other vital information. Thus, the records of each individual identified from the accession list will have to be pulled to determine if he qualifies for inclusion in the study. This eligibility assessment will be done at the records center and coordinated by the 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 staff have visited the St. Louis center and reviewed a systematic sample of 101 Army personnel records. The records were chosen to encompass those accessed by the Center from 1966 through 1973. Of the 101 selected, 1 was missing, 3 were checked out, and the contents of 4 could not be interpreted by CDC staff. Sixty-one of the remaining 93 were single-term draftees and enlistees; 24 of the 61 single-term soldiers served in Vietnam, 10 served in Europe, 8 in Korea, 16 in the U.S. only, and 3 elsewhere. This work indicates that the approach can yield a sample with relatively little wasted effort, and CDC believes 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 selected from among those soldiers whose personnel folders were acquired by the records center during 1965-1977; those chosen will have entered military service in 1965-1971 and will have served in Vietnam during the years 1966-1972. For the Vietnam service cohort this should provide a year-of-tour distribution roughly proportional to the year-by-year Army troop strength in Vietnam over the period 1966-1972. The selection procedure for the control cohort will be such that its period of service distribution is equivalent to that of 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 three groups: (1) men who served only in the continental U.S.A., (2) men who served in the U.S.A. and Europe, and (3) men who served in the U.S.A. and Korea. The numbers of men in these three groups will be proportional to the military strengths in the three areas in 1966-1972. AAOTF will give CDC the same sort of information about each soldier in this study as will be provided for those men in the Agent Orange study, except that no daily geographical location information will be given.

4.1.3. Selected Cancers Case-Control 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 is recommended 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 the selected cancers 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 the case group, and this will allow disease incidence rates to be estimated by veteran status.

It is proposed to use the Surveillance, Epidemiology, and End Results (SEER) Centers, sponsored by the National Cancer Institute, as the major source of cases. The SEER Centers ascertain nearly all people newly diagnosed with cancer in 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. CDC has contacted eight of the SEER Centers by telephone and they 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, each center employs 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 that investigated the association of bladder cancer with artificial sweetener use (Hoover and Strasser, 1981) and uterine, ovarian, and breast cancer with oral contraceptive use (Layde et al., 1983). Other population-based cancer registries may be used 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 the selected cancers 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 6 months of diagnosis. Men in this age group have been selected because they were of military service age during the years herbicides were used in Vietnam (see section 4.4.2). Since soft tissue sarcomas are so rare, CDC has considered including additional cases diagnosed before July 1, 1984, in order to increase the power of the study to detect any association which may be present between herbicides and/or service in Vietnam and sarcomas. This possibility has been rejected for three 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 that arose before 1984 might give only an illusion of increased power. 2) Because the fatality rate for soft tissue sarcoma is quite high (Tucker and Fraumeni, 1982), information about early cases and controls would frequently have to be gathered from next-of-kin instead of from the affected man. However, this latter point would not be a major concern if data collection for these cases were limited to relatively simple items, such as whether the man served in Vietnam. 3) The New York State Health Department has completed a sarcoma study for cases diagnosed in 1962-1980 and the VA and the Armed Forces Institute of Pathology are planning a study directed at cases diagnosed in 1975-1980.

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 blocks on each case and will establish their own diagnosis without knowledge of the presumed diagnosis. Interviews with cancer cases will not be delayed for confirmation by the pathology review panels.

Controls will be selected 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 (NCI) Bladder Cancer Study (Hoover and Strasser, 1981) and CDC's Cancer and Steroid Hormone Studies (Layde et al., 1983). Over 90% of the 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, as detailed in Appendix C, 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 believes that the effect of this potential bias will be small for two reasons: 1) our control group will be so large that some very poor people will be included; and 2) an analysis stratified by socio-economic status should help ameliorate whatever bias is present. On the basis of the age and race distribution of cases, CDC will select controls from the list of eligible men so 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 what is expected, control selection can be modified.

4.2. Location of Study Subjects

For each of the veterans selected for the Agent Orange and Vietnam Experience studies, CDC will receive from the AAOTF a variety of identifying information with which to begin the location process. The information available for each man will, in addition to his full name, include: his Social Security Number (SSN) and service number; the address he gave the military at discharge; the name and address of one parent and the name and address of one sibling (the names and addresses of relatives are not invariably available in the records). Although this may seem to be a substantial amount of information with which to begin tracing, the addresses will be about 15 years old, and CDC expects to experience great difficulty in locating individuals -- indeed CDC believes that this could present such a formidable obstacle that it may not be possible to complete these studies using the sample selection strategies proposed here (see section 4.4.1. regarding minimum acceptable participation rates and section 4.5.1. for a discussion of the role of the pilot studies). If it should turn out that these two cohort studies are not feasible, CDC would propose another plan for the Vietnam Experience study, but an Agent Orange study should start with military unit records. The alternative plan for the Vietnam Experience study would involve sample selection by a variant of the RDD technique described in section 4.1.3 for the Selected Cancers Study. However, this alternative plan would involve considerable expense in identifying the requisite number of veterans.

The Air Force's Ranch Hand Study team had great success in locating its study subjects -- 97% for the Ranch Hand group and 93% for the control group. This gives CDC a standard to reach for, but there will be marked differences between the Ranch Hand subjects and the subjects selected for CDC's two cohort studies. About 25% of the Ranch Hand sample was still on active military duty at the time data were collected and another 25% was composed of men retired from the Air Force (and therefore receiving pension payments). Thus, the location of about 50% of the Ranch Hand study sample was known before the study began. Very few of the men selected for the Agent Orange study are expected to be on active duty at this time, and none of the Vietnam Experience study subjects will be, because they are to be chosen from the St. Louis records center (section 4.1.2).

The one reason for optimism is that SSNs will be available for virtually all those chosen for the two cohort studies. CDC expects that the major locating source will be the Internal Revenue Service (IRS). CDC will submit the names and SSNs of the desired veterans to the IRS which will return to CDC the most current addresses available. This should be a very good source, but there are inherent limitations. Most importantly, the IRS has current addresses only for persons who have recently filed tax returns; IRS will remit addresses for individuals who have not paid taxes for some time, but it will not indicate whether the addresses are current. It is obvious that if some veterans (or more importantly the aggregate of veterans in one of the study groups) are operating on the margin of economic life, they will be difficult to locate. The SSNs will also be transmitted to the Social Security Administration (SSA), which can let CDC know if a man is deceased and, if not, if he has recently been paying social security taxes and who his employer has been (CDC experience in using SSA records for tracing indicates that the records used for this work may be out of date by 2 or 3 years). SSNs may also be given to the Veterans Administration which can check to see if a death benefit has been paid. Furthermore, the SSNs will be used for future mortality followup (see section 4.3.1.1) through the National Center for Health Statistics' (NCHS's) National Death Index.

If the simple approaches described above fail to locate a study subject, then much more labor-intensive, difficult, and expensive procedures must be used. These procedures will almost certainly involve field "detective" work and the use of such sources as credit bureaus and contacts with neighbors at the last address of record.

Because of the design of the Selected Cancers Study, CDC does not anticipate that the location of study subjects will present significant problems.

4.3. Ascertainment of Health and Exposure Status

A variety of health and exposure data will be collected for each of the participants in the two cohort studies and in the Selected Cancers Study. The categories of items to be collected and the methods by which they are to be gathered are presented below; Appendices D-E contain relatively specific topical lists of items of interest. The specific items to be included in questionnaires and examinations may be modified because of new findings from studies now in progress (e.g., Ranch Hand; see also section 4.6.1).

4.3.1. Agent Orange and Vietnam Experience Studies

4.3.1.1. Mortality Information

It is projected that the first component of both cohort studies to be completed will be mortality assessments. It is proposed that mortality assessment of the five different cohorts be repeated every 5 years for an indefinite period of time through use of NCHS's National Death Index. During the main studies, the fact of death will be ascertained in the course of attempts to locate the selected veterans (section 4.2). As noted before, the name and SSN of any study subject who does not appear on the returns from the IRS or who cannot be located will be submitted to NCHS, SSA, and VA. The NCHS can provide help through the National Death Index for those who died after 1980. SSA or VA should also be able to indicate which veterans are deceased and, in addition, may be able to provide locating leads for subjects who are still living. The VA's Beneficiaries Identification and Records Location System (BIRLS) files will be particularly useful in identifying veterans who died before 1981. In 1981, veterans' burial expenses provided by the VA were reduced, and there may have been reduced reporting of veterans' deaths to the VA after that change. In addition, some deceased may be identified by relatives or neighbors who are contacted during the location process.

During the study CDC will estimate the degree of underascertainment of deaths by extensions of the capture-recapture methods used by ecologists (Hook and Regal, 1982). There are unlikely to be enough deaths among veterans in the pilot sample, however, to assess accurately the completeness of identification of the deceased before the full-scale study.

Once the fact of a death has been ascertained, CDC will proceed to obtain records that will help to establish the cause. Death certificates will be routinely obtained, usually from the vital records department of the state in which the death occurred. In order to provide the most powerful assessment of mortality, it is important to have accurate accounts of the causes of death, and death certificates suffer in this regard -- they are only accurate for rather broad cause groupings. This quest for accurate cause-of-death information is considered to be particularly important at this point, since the numbers of deaths in this group of men is, on the basis of U.S. mortality statistics, expected to be small (Table 1). Therefore, when possible, hospital records, autopsy reports, and other documents that will help establish the cause of death will be obtained. Mortality data will be analyzed in two ways: first using only death certificate information, and second using the supplemented certificate data.

In the course of selecting the cohort members, those who were killed in action will be ascertained; this will give us one measure of the combat intensity to which members of the various cohorts were subjected.

4.3.1.2. Morbidity and Exposure Information

Data regarding the morbidity experience of the study subjects will be collected through health interviews and medical and psychological examinations and through selected laboratory tests.

4.3.1.2.A. Health Interviews

CDC proposes to conduct personal interviews with all study subjects who agree to participate in the studies (6,000 per cohort). These interviews will be conducted by telephone by specially trained interviewers. Telephone interviews may be supplemented by in-person interviews if the pilot study indicates that participation may be suffering because too few study subjects can be reached by phone (about 95% of U.S. households have phones). It is anticipated that the interviews will be done by using a "computer assisted telephone interviewing" (CATI) system. CATI has numerous advantages over the traditional paper and pencil telephone or in-person system. Most importantly, CDC believes that much better quality control is possible when a CATI rather than a traditional system is used. Examples of the enhanced quality control include data checking and editing while the interview is in process, modification of the questionnaire to fit the individual respondent, automated implementation of interview skip patterns, and the ability to monitor the interviewers' transcription of respondents' answers to questionnaire code (i.e., the interviewers' video displays can be watched on a monitor, by an authorized supervisor, at the same time audio monitoring is done).

It is hoped that two interviewers can be used to conduct each veteran's interview. One interviewer will ask questions about military service and other exposure-related matters and the second will ask questions about health and other outcome-related issues. The purpose of using two interviewers is to keep the interviewer questioning about health "blind" to the "exposure" status of the veteran being interviewed.

During the next few months, CDC staff and outside consultants will design the formal interview instruments, including the detailed wording of questions. The general types of questions are explained below, and a topical list of items to be included in the interviews can be found in Appendix D.

Questions will be asked about a wide variety of health outcomes and also about exposures and behaviors which may predispose to ill health. Some variables in the latter category may be confounding factors — factors which may be associated both with health outcomes and with exposure (cohort) status. For example, race is a risk factor for many diseases and may be associated with cohort membership. If the proportions of blacks and whites in the several cohorts are not equivalent, a race effect could be confounded with, or mistaken for, a cohort effect for any health outcome where race is a predisposing factor. Therefore, race needs to be ascertained during the interviews so that if an imbalance is present, it can be accounted for during data analysis (section 4.6.2). In addition, a limited number of questions will be asked about each subject's military experiences. Apart from basic administrative data, we have categorized the items to be included in the interviews into four categories. Examples from each of these groups are presented below, along with a brief rationale for collecting such information.

--Sociodemographic Information

Variables in this class include race, place of residence, marital history, problems in obtaining employment, occupation, income, and education. Most of these variables are potential confounding factors, as discussed above, and are therefore required for analysis. In addition, some of these social

characteristics are themselves possible effects of service in Vietnam and are therefore of interest as psycho-social outcomes.

--Medical History

This area forms the heart of the interview. The concerns veterans have expressed about their health have been wide ranging -- numerous types of complaints have been heard. There are no strong hypotheses which can guide our inquiry, and it must be therefore thought of as being essentially descriptive. However, there are certain pointers from animal experimentation, from industrial exposures, and from the lay press which can guide us so that we do not overlook areas of concern. And our regular monitoring of comparisons between the various cohorts for major health outcomes will allow us to generate specific hypotheses and supplement or expand on certain lines of questioning as the study progresses (see section 4.6.1). In addition to the standard closed-ended questions about major health outcomes, the interview will provide an opportunity for open-ended responses to queries about what concerns individual respondents have about their health. These answers will be monitored at regular intervals so that anything striking can be included in interviews with later respondents. In the Agent Orange study more emphasis will be given to dermatologic and immunologic outcomes, whereas in the Vietnam Experience study more emphasis will be given to psychologic outcomes.

--Environmental and Occupational Exposure Information

A wide variety of potentially harmful exposures are included in this class. Examples include those questions about occupational exposure, particularly to herbicides, smoking, alcohol, and illicit drug use. Some of these factors are accepted as risk predictors for certain diseases, but while some are only suspected. In addition, some of these factors may be associated with service in Vietnam, and therefore are potential confounders.

--Military History

A substantial amount of information about study subjects' military service will be available among the data provided to CDC by the AAOTF, but many important items will not. Specific areas which will require inquiry during the interview include an inquiry about occupational duties while in the military (to supplement the military occupational specialty designation which will be provided by the AAOTF), a scale to rate the intensity of combat to which individuals were exposed, and the study subjects' perceptions about exposure to herbicides. The combat scale will not be applicable to interviews done with the non-Vietnam service cohort included in the Vietnam Experience study, nor will questions about perceptions about exposure to fixed-wing herbicide applications.

Two additional comments need to be made regarding the development of the questionnaire. First, because of the varied educational and cultural background of the veterans, care will need to be taken to ensure that participants understand all the questions. Second, the order of the inquiries on the questionnaire will not necessarily reflect that of Appendix D. Both the wording and structure of the questionnaire will be extensively evaluated during the pretest and pilot phases (see section 4.5.1).

4.3.1.2.B Medical and Psychological Examinations; Laboratory Tests

A random subset from each of the five study cohorts will be selected for participation in the medical, psychological and laboratory work-ups; the goal is to complete examinations on 2,000 men per cohort. The examinations will take about 2 days to complete and will be done in as few centers as feasible to minimize problems of standardization of methods among the centers. CDC would prefer one or two examining centers, but the availability of contractors capable of the necessary through-put is unknown; moreover, travel to distant locations may enhance or detract from obtaining a reasonable level of participation (see section 4.5.1.2). The selection of subjects for each of the centers (if there is more than one) could depend upon geography, or the selection could depend on which study the individuals are participating in, but this cannot be specified until the pilot studies and pretests are complete. It is hoped that one laboratory can be used to perform most tests.

The items to be included in the examinations and the laboratory tests to be used are listed in Appendix E; as explained in section 4.6.1, this list could be modified, if indicated, by the results of the interviews or the early examinations. The lack of strong hypotheses mentioned above makes a relatively wide-ranging battery of tests and procedures necessary. In addition, the medical examinations and laboratory tests will be of high quality and fairly comprehensive as a service to the study subjects and to enhance the chance of achieving a high participation rate.

Because of specific concerns about psychological disorders, especially post-traumatic stress disorder, a fairly extensive psychological and neuropsychological battery of tests will be used. The guiding principle in the choice of tests in this area was the need for well-standardized tests that yield numerical, not just qualitative, data. The neuropsychological tests measure visual and auditory perception deficits, learning and memory impairments, and attention, coordination, and dexterity abnormalities. The psychological tests focus on personality assessment, current symptomatology, and a standardized diagnostic screening procedure.

To detect neurological and immunological deficits, some rather specialized procedures will be included. However, CDC's general approach will be to limit the examinations and tests to those that measure health and well-being deficits in the simplest and most direct way possible. For example, fertility problems will be evaluated in the interview (above) and in the history taken at the time of the examination rather than by the examination of sperm morphology and motility or gonadotropin assays. Only if the interview data suggest an average deficit in fertility in one or more of the cohorts will more elaborate testing be undertaken (section 4.6.1). The CDC study team also takes a skeptical attitude to such esoterica as the examination of peripheral blood cells for chromosome breaks -- in this case one is at a loss to know what prognostic significance can be attached to chromosome breaks and other such abnormalities. If a test does not help a physician to make a diagnosis or if it does not itself indicate outcomes are associated with health and well-being or longevity, then the test will not be used. However, if more sensitive, specific, and reliable tests for the outcomes of interest become available during the course of the study, we will consider their feasibility and use in random samples of those selected for physical examination and laboratory testing.

All medical examinations at each center will be done by physicians trained in appropriate specialties. When necessary, the examining physician will consult with another specialist (e.g., a neurologist or dermatologist). Examinations for which there may be substantial inter-observer variation will be done by one examiner at each center. The various examiners will be "blind" as to which cohort individuals belong. Quality control for laboratory tests will be done by the contractors' laboratories and monitored by the CDC staff. Study participants will be informed of the results of the examinations for those items where such knowledge will be of benefit to the individual veteran. (Some tests, particularly in the psychological area, may have little meaning for the individual because they are not designed for the purpose of making individual diagnoses.) If the study examinations raise suspicion about disease and extensive diagnostic work-up is required for definitive diagnosis, then the individual will be informed of the need and referred to the health-care provider of his choice, with copies of the pertinent portions of the evaluation. In such cases, CDC does not propose to complete definitive diagnostic workups, since this is more appropriately coordinated by the physician who will be caring for the veteran.

4.3.2. Selected Cancers Case-Control Study

The information to be gathered in this case-control study is outlined below, and a detailed topical list is found in Appendix F. As for the two cohort studies, the actual interview instruments will be prepared over the next few months. CDC prefers that interviews for this study be done by telephone from a central location, using CATI (see above). If this is done, then the interviewer who collects most of the interview information can be "blind" as to the respondent's case/control status. However, participation by the various cancer registries will probably not be high unless they can use their own staff to do the interviews (this was the approach CDC used in its Cancer and Steroid Hormone Study). If the latter approach turns out to be necessary, then the use of CATI may not be feasible, although CDC will explore the possibility of implementing a CATI system on a microcomputer. Since survival is short for some of the cancers included in this study, in some instances next-of-kin may need to be interviewed.

Information which will be gathered about known or suspect risk factors for the selected cancers is divided into five major groups. Examples from each of these groups are presented below, along with a brief rationale for collecting such information.

In addition to the information about military service which will be collected during the interviews, the AAOTF will assist in making an estimate of the herbicide exposure likelihood for each Vietnam veteran case or control (AAOTF will not know the case/control status of the individual veterans when making this assessment). The exposure likelihood estimation process will be similar to, but much simpler than, that proposed for the Agent Orange study. The technique is similar in that it will depend on the proximity of individuals in time and space to herbicide applications. It is simpler in that the specificity with which this proximity is to be measured will be much lower than that proposed for the Agent Orange study. Specificity will be less because the records review needed to duplicate the Agent Orange technique would be especially burdensome -- the veterans in this study could come from any one of the four branches of the military and from any unit stationed in

--Sociodemographic Information

The type of data and rationale is essentially the same as that for the Agent Orange and Vietnam Experience studies (see above).

--Family History of Cancer

Soft tissue sarcomas and lymphomas have been reported to cluster in families. This tendency may be genetic or may reflect a persistence of adverse environmental circumstances in families, or both. The tendency of cancers to recur in families is not likely to be strongly related to service in Vietnam and therefore should not confound the analysis of cancer risk associated with that service. However, the risks of familial occurrence are not well known in the U.S.A., and this information will be useful for other reasons.

--Medical History

Underlying diseases which may predispose to the development of these tumors include rheumatoid arthritis, other cancers, celiac disease and gluten enteropathy, radiation or immunosuppressive therapy, diphenylhydantoin therapy for lymphomas (Grufferman, 1982; Greene, 1982), and immunosuppressive and radiation therapy for soft tissue sarcomas (Tucker and Fraumeni, 1982). Primary and acquired disorders of the immune system have frequently been associated with the development of these tumors. A medical history with specific questions regarding these risk factors will be included in the questionnaire. In some situations additional medical information may be needed to establish with certainty the underlying diagnosis. On an as-needed basis, the cancer registries will be responsible for retrieving additional information on the medical evaluation of these underlying medical disorders, including workup, histologic diagnoses, and/or histologic specimens.

--Environmental and Occupational Exposure Information

A wide variety of potentially harmful exposures are included in this class. Examples include those questions about occupational exposures, contact with animals, smoking, and illicit drugs. Some of these factors are accepted as risk predictors for cancer, but some are only suspected of being such. The following chemicals may be related to soft tissue sarcoma: arsenicals, vinyl chloride, and iron dextran injections (Tucker and Fraumeni, 1982). Halomethane, lead, asbestos, and cadmium may be related to lymphomas (Grufferman, 1982; Greene, 1982). In addition, some of these factors may be associated with service in Vietnam (e.g., alcohol or drug abuse hepatitis exposure).

--Military History

Information collected about the military service of the cases and controls included in this study will be similar to that collected during the two cohort study interviews.

4.4 Sample Sizes, Statistical Power, and Participation Rates

4.4.1. Agent Orange and Vietnam Experience Studies

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 6,000 men. The number 6,000 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 1,000 in comparisons of two cohorts (if there is little or no misclassification in the selection of men for the cohorts) (see Table 2). A high β level, equal to the α 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 2,000 be selected from each of the cohorts for the medical, psychological, and laboratory phases 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% (see Table 2).

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 (see Table 3) in populations similar to the veterans to be 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 under way 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 that they are appropriate to detect an increased risk of important health outcomes in exposed veterans. For example, on the basis of data from the SEER network 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. 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. On the basis of HIS and HANES data, 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 2 x 2 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 (see section 4.6.2.) and if unnecessary variables are inadvertently included, this may reduce power. 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 that may reduce power is misclassification on the variables used to define the cohorts ("exposure" variables) -- if the misclassification is random. Of particular concern is the possibility that the records that 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 of 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 to 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.

To achieve the power desired in the interview phase, it will be necessary to begin with cohorts larger than 6,000 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 an 85% interview rate among those located, for an overall participation rate of 72%. Therefore, CDC recommends that the AAOTF select 8,350 (approximately $6,000/0.72$) veterans for each of the cohorts.

If the interview phase is successful, it should not be difficult to obtain the cooperation of 2,000 men per cohort for the examination phase, since there will be a pool of 6,000 to draw from. 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 2,000 per cohort but rather that participation might be limited to a highly selected group of men. We believe 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. As noted in section 4.2., CDC believes 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 believes that inferring directly from this experience to its own situation probably gives a somewhat optimistic expectation. The NCHS examinations were done in trailers 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 (see section 4.3.1.2.). Moreover, the NCHS sample included persons of both sexes and all ages, whereas CDC's

cohorts will be composed wholly of men of a narrow age range, a group that 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. Although not ideal, such comparisons may provide insights into the characteristics of those refusing to participate and those not located.

4.4.2. Selected Cancers Case-Control Study

As with the cohort studies, the power of this study to detect a real increased risk among Vietnam veterans will depend 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, section 4.1.3.), and the magnitude of the increased risk. To maximize the possibility for including veterans who could have been exposed to Agent Orange in Vietnam, the study sample will include only men born from 1929 through 1953. Men born during these years ranged from 18 to 35 years of age during the time of maximum U.S. involvement in Vietnam, 1964 through 1971. Not including men with birth years before 1929 is expected to result primarily in the exclusion of non-combatant commissioned and non-commissioned officers, veterans who can be presumed to have had a low likelihood of exposure.

By using VA data, the overall prevalence of service among men who will be 30-54 years of age in 1986 in the SEER areas has been estimated as 7.4% (Table 4). Power calculations for a 2-fold increase in risk among Vietnam veterans in general are presented in Table 5. Ages 30-54 are chosen as a reasonable approximation to the ages of men born 1929-1953. We have decided to study about 1,300 controls (i.e., equal to the projected numbers of lymphoma cases), since this number will give fairly good sensitivity for a 2-fold increase in risk for Vietnam veterans in general and since adding further numbers to the control sample will do little in terms of improving the power.

The computation of power to enable the detection of a 2-fold increase in risk for Vietnam veterans in general requires explication. The Swedish studies which have suggested an association between herbicide exposure and sarcomas found risk increases of about 5-7. Thus, it would be reasonable to base power calculations for this study on relative risks of this magnitude and on an estimated prevalence of "meaningful" exposure among Vietnam veterans. As discussed elsewhere in this protocol, the records available for exposure estimation are not sufficient to allow a determination of "meaningful"

exposure. Therefore, CDC has designed the study to be powerful enough to detect a generalized increase of 2-fold among all Vietnam veterans. However, Table 5 also includes power calculations made on assumptions that various fractions of Vietnam veterans might have been exposed. The power of the Selected Cancers Study for lymphomas will be higher than for sarcomas because the number of cases is larger. Likewise, the power to detect increases in risk for liver, nasal, and nasopharyngeal cancers will be lower because of smaller numbers. It is unlikely that small real increases in risk can be demonstrated, even for lymphomas. Moreover, if Agent Orange or some other factor really has increased the risk of exposed veterans a small amount, and if only a small proportion of veterans were exposed to a toxic dose, the sensitivity of this study will be much lower than the figures presented. This will be a large case-control study, based on all soft tissue sarcoma and lymphoma cases that have occurred in a population of about 3,769,000 males aged 30-54 over a period of 4 years. Viewed from a somewhat different perspective, it will have roughly the same sensitivity as a very, very large cohort study, the cost of which would far exceed the cost of the proposed study.

4.5. Pretests and Pilot Studies

4.5.1. 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 evaluating 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 will be 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 would be necessary to repeat the

process with 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 straightaway for the main studies.

An example of the pretest approach is the evaluation being done now to assess the locatability of male veterans and the plans for making the same sort of evaluation for female veterans. The AAOTF has transmitted to CDC identifying information for some 840 male veterans, and CDC has 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. If the result of the locating pretest on this sample is encouraging, CDC will believe that the locating process does not need to be tested further before it embarks on the pilot study (see below). On the other hand, if the result is clearly discouraging, then CDC might recommend another study approach (see section 4.2.). In either case, time could be saved and delays in reporting results to veterans held to a minimum.

4.5.1.1. 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 seems in order, particularly to evaluate any problems that might arise in attempting to make the non-Vietnam veteran cohort match the Vietnam cohort in regard to calendar years of service (see section 4.1.2.). To this end, a pretest sample of 200 Vietnam veterans and 200 non-Vietnam veterans will be chosen. If serious problems are identified with the procedures, then the process will be repeated with corrected procedures. The samples of veterans gathered during the (ultimately) problem-free pretest will be used as a part of the pilot study (see below).

Much work needs to be done with the records that will be used to classify exposure. Although 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 that 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 on the randomly chosen days (see section 4.1.1.). 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 (section 4.1.1.); 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