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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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Atlanta, Georgia 30333

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U.S. Department of Health and Human Services
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NOTICE

At the time this document was printed (December, 1983) these protocols had not yet received approval for protection of human subjects from the Institutional Review Board of the Centers for Disease Control, nor clearance by the Office of Management and Budget. Both approvals are required for implementation of the studies described in this document.

CENTERS FOR DISEASE CONTROL

Protocol for Epidemiologic Study of the Health of Vietnam Veterans

Contents

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 forseeable 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 strudy, 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 emanataed 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
Service Experience	A	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

Vietnam. The simplified technique is being developed by CDC and AAOTF for CDC's birth defects study.

--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 beta level, equal to the alpha level, is suggested since CDC believes that as much attention should be given in these studies to type II errors as to type I errors. CDC further recommends that a sample of 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

individuals for the main studies. Later, the encounter scoring scheme will be tested again for individuals.

4.5.1.2. Location Rate, Participation Rate, and Instrument Assessments

As mentioned above, some parts of the evaluation of the locatability of the cohort study subjects are now under way. This will continue as a part of the pilot study. Besides providing more information about locatability, the cohort pilot study will give information about expected main study participation rates and about possible difficulties with the interview instrument and examination protocol. The pilot study will be nearly a main study in miniature, the major exception being that the proposed selection process for the Agent Orange study cohorts will not be used to choose any of the pilot study subjects. As mentioned above, the subject selection process for the Vietnam Experience study will provide 400 veterans for the pilot study. Rather than wait for the process of ranking the companies in the 50 battalions from III Corps to be completed before selecting a pilot sample for the Agent Orange study, CDC recommends another approach to save time. It is proposed to simulate the Agent Orange main study through the use of 400 veterans who will be chosen from among the 110-120 combat battalions stationed in III Corps during 1967-1968.

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

As noted elsewhere, CDC is concerned that it may be difficult to reach an acceptable level of participation in the examination phases of the studies. The Ranch Hand study group's enviable success in this regard is attributed in large measure to their treatment of study participants as "VIPs." CDC will attempt to duplicate this treatment. Since monetary factors may influence participation in the examination phase, CDC will test the effect of recompensing the subjects for lost wages; offering recompense may help to raise participation or if the offer offends a sense of altruism, it may decrease it. In addition, the effect of travel to distant locations for the examinations may enhance or deter participation. If it appears that more than one examining center will need to be used in the main studies (see section 4.3.1.2.), the effect of distance to the center will be tested in the pilot studies.

4.5.2. Selected Cancers Case-Control Study

The Selected Cancers case-control study will be given a full pilot study in 2-3 SEER centers, each using 10 cases of lymphoma and 20 controls. Only lymphoma cases will be used because of the rarity of cases of the other cancers, and CDC cannot risk "wasting" them on a pilot study. Only 2-3 SEER centers will be used to minimize the time required -- CDC believes that more are not required because of its previous success with the Cancer and Steroid

Hormone study. The main purpose of a pilot study will be to evaluate the participation rate of males aged 30-49 and the interview instrument (CATI will not be developed for this pilot study, see section 4.3.1.2.). The work done by the AAOTF on scoring herbicide exposure likelihood for CDC's birth defects study (section 4.3.2.) is considered a valid surrogate for an assessment that could be done specifically for this study.

4.6. Data Analysis and Quality Control

4.6.1. Timing of Analyses

The preferred approach to the timing of the analyses and the release of findings from the cohort studies is not easily found. Veterans will have considerable interest in receiving information about study results as soon as possible, and this suggests early analysis and release of significant findings even while data are being collected. But there are dangers in this approach. Locating individuals for the cohort studies can take considerable time, and, therefore, the early participants will be those who are easy to locate. One may speculate that the health of those who are easy to find differs from those who are difficult to find. If this is so, then early analysis could give a misleading picture and, ultimately, release of such results could be damaging.

Although this consideration is cause for reluctance to make early analyses, it is also desirable to keep open the option of changing the interview instrument and examination procedures to accommodate some relationships noted in early interviews and examinations. In effect, the study itself could be used to generate hypotheses as well as test them. Having the flexibility to add procedures or questions to the examinations and interviews would also make it possible to accommodate new hypotheses which derive from sources outside these studies (examples of such outside sources include the VA's Agent Orange Registry, the Ranch Hand study, CDC's study of people exposed to dioxin at Times Beach, Missouri, the Australian studies of veterans, and the studies of U.S. Vietnam veterans being conducted by several state health departments). Given the lack of strong hypotheses at the outset, this is attractive. Biases could result from changing procedures if the changed procedures were disproportionately applied to difficult-to-locate individuals. To avoid this problem, CDC will divide the study subjects into groups for release for location and interview on a monthly basis. Changed procedures will only be used for those groups that have not yet been released at the time the changes are made.

On balance, CDC believes that it is best to do analysis on a regular basis as the data are collected and to use the results to amplify or correct the thrust of the investigation. No findings will be released before all data collection and analysis is complete for some particular study phase, unless CDC, in consultation with its steering committee (section 9.), determines that it is mandatory that the preliminary analyses be released. An example of a finding which could not be withheld would be a convincingly substantial increase in the risk for a serious disease, especially if there are possibilities for effective treatment if the malady is diagnosed in its early stages.

The concern about possible differences between study subjects who enter the cohort studies early and late does not apply to the Selected Cancers study. Therefore, CDC does not have the same level of concern about early release of findings from the case-control study. However, early findings which are released and later modified by further data collection will be difficult for the public to understand. On balance, CDC recommends the same approach as suggested above for the cohort studies.

4.6.2. Summary of Analytical Approach

The two types of studies use somewhat different philosophical and analytical approaches to reach the same end, viz., the comparison of the risk of contracting certain diseases in those exposed to herbicides (and/or Vietnam service) with those not exposed. The two cohort studies provide direct estimates of disease incidence or prevalence, since the studies will begin with men who are selected because of some "exposure." Case-control studies usually do not provide estimates of disease rates or risks. However, the Selected Cancers study, being a population-based case-control study, will provide some insight into the incidence of the specified cancers among Vietnam veterans and among other men. This statement should not be taken to imply that this approach is equivalent to a cohort study, since the base population data is estimated by a random digit dialing census and could be influenced by incompleteness of the census because of lack of telephones and by migration.

It is anticipated that a major part of the analyses will focus on the association between the presence or absence of disease and Vietnam service and herbicide exposure. For this part of the analysis, the primary measure of association will be the odds ratio, and the analytical techniques used will be those appropriate for dependent variables that are categorical. Other analyses will focus on dependent variables that are continuous and more appropriately dealt with by such techniques as the analysis of variance (Scheffe, 1959; Anderson, 1958) or non-parametric analogues (Puri and Sen, 1971). For example, a traditional approach to the data to be derived from some of the psychological tests would be to use multivariate analysis of variance as the primary analytical tool. For the sake of brevity, categorical data analysis is emphasized in the description that follows. However, it is to be noted that different but analogous techniques will be used for analyses involving continuous dependent variables.

It is desirable that the measures of association (e.g., odds ratios) should be as free of the effects of other variables as possible; in other words, the estimates should be free of confounding effects. Therefore, the initial phases of analysis will be a search for factors that confound the estimates of association. This is not a simple matter.

A primitive way to approach the problem is to compare (for a specific health outcome, exposure status and potential confounding variable) the crude odds ratio with the odds ratio adjusted for the potential confounder. If the two odds ratios are substantially the same, then the variable is not a confounder, at least within the study data, and need not be considered further. If it is determined that adjusting for the variable does alter the odds ratio in the data at hand, then it must next be determined if the variable independently predicts disease and exposure. If it does independently predict, then the variable will be included in further

analyses. If, on the other hand, the prediction is not independent, then the variable may be a part of the causal chain and it should not be used as an adjusting variable. To illustrate, suppose we consider education as a potentially confounding variable in one of the cohort studies. The first step would be to determine if adjusting or "controlling" for education changes the odds ratio substantially. If not, then education can be ignored in further analysis of the specific disease-exposure relationship. If adjusting for education does substantially alter the odds ratio, then it will be determined if education is related to disease within the "exposed" and "unexposed" groups, that is, it will be determined if education predicts for disease independently of exposure status. If education is only related to disease through the agency of cohort status, or vice versa, then it may be omitted in further analysis.

The flaw in this approach is that there may be other variables which modify the association between the variables being considered pairwise (i.e., in statistical jargon, higher order interactions). For example, education may be associated with memory of key factors which are, in turn, associated with disease and service. Thus, this primitive approach to discovering confounding variables has merit primarily because of the ease with which it may be accomplished and because it can be used for categories of disease with relatively small numbers (see also below). Under these circumstances, the final estimate of the effect measure for a particular classification of disease would be done by a method such as that of Mantel and Haenszel (1959). This procedure will yield a summary odds ratio and test statistic (or related confidence limits) for the several 2 x 2 tables (Vietnam Experience study example)

		Vietnam Service	
		Yes	No
	Yes	a	b
Disease X			
	No	c	d

which have been formed on the basis of one or more confounding variables.

A better (but not infallible) way to perform a detailed assessment of variables which influence the association between Vietnam service and cancer is to consider them in a multivariate framework. The analytic technique to be used will be log-linear analysis or a related technique, such as logistic regression or proportional hazards modelling (Bishop et al., 1975; Breslow and Day, 1980; Cox, 1970). The basic approach can be illustrated by considering the simple case of a 2 x 2 x 2 table with race as the third variable of concern:

		White Vietnam Service		Black Vietnam Service	
		Yes	No	Yes	No
	Yes	a	b	a	b
Disease X					
	No	c	d	c	d.

It should first be determined whether the odds ratios in whites and blacks are substantially the same (i.e., does race modify the association between service and the disease). If the odds ratios are not substantially different then one need only consider the association between service and disease (with possible adjustment for confounding). If the odds ratios are substantially different, in whites and blacks, the association between service and disease should be considered separately for each race.

In actuality, the problem will be much more complex. Many variables are potential confounders or modifiers of the association between various diseases and service, and, consequently, it will be necessary to consider numerous 2 x 2 tables. Although analysis by such methods as logistic regression is, in theory, well suited for this problem, difficulties will arise. Stratification over increasing numbers of variables rapidly produces so many 2 x 2 tables that there are no observations in many table cells. The method then begins to break down.

We, therefore, have to make some compromise between the desired degree of stratification and search for confounding and higher order interactions and what will be practicable within the framework of these studies. In summary, we propose to do our analyses starting with the simple stratification techniques on relatively limited numbers of variables and, as we learn more about the data, we will progress to control of confounding and model building by the more ambitious logistic regression or related techniques.

4.6.3. Quality Control

The success of the above methods of analysis in assessing the association of herbicide exposure and Vietnam service with adverse health outcomes is predicated on the accuracy of the data being analyzed. CDC has conducted many nationwide epidemiologic studies and is experienced in dealing with the important issues of quality control and data validation.

Many of our approaches to these issues have already been mentioned. For the Agent Orange study CDC has requested that the National Academy of Sciences make a further assessment of the critical information on herbicide applications contained in the "Herbs" computer tape (see section 4.1.1). For both the Agent Orange and Vietnam Experience studies, we will attempt to achieve rigid quality control for both the laboratory testing and physical examinations (section 4.3.1.2.B) and the questionnaire administration. Central to the latter effort will be our use of computer-assisted telephone interviewing (CATI) (section 4.3.1.2.A). In addition, for the mortality analysis for these studies we will assess the extent of underascertainment of deaths for each of the cohorts (section 4.3.1.1).

Among our quality control measures for the Selected Cancers study are an expert panel review of the histologic material used for diagnosing the cancer (section 4.1.3) and blinding both the CATI interviewers and the AAOTF personnel responsible for assessing Agent Orange exposure as to the case or control status of the study participants (section 4.3.2).

In addition to these approaches, emphasis will be given to evaluation of non-participants (section 4.4.1). Where feasible, we will attempt to verify a sample of hospitalizations and participant-reported illnesses with the

relevant health care providers. We will take special care to ensure standardization of methods if more than one examination and/or laboratory center is needed (section 4.3.1.2.B). These efforts will include evaluating volunteers at more than one examination center to assess the between-center variability.

CDC is committed to conducting the best possible assessment of the health of Vietnam veterans. We will make every effort to obtain the best quality information on the health of study participants. Where possible, we will assess the extent of any inaccuracies in our data.

5. Inferences from Possible Study Findings; Study Limitations

A major concern of Vietnam veterans is that they are at high risk for quite a variety of diseases. The cause of this putative high risk is generally suspected to be exposure to Agent Orange and other herbicides, but there is also concern that other factors incidental to Vietnam service may have conferred an increased risk. The design of CDC's studies should permit an assessment of both general and some specific concerns. The Agent Orange study will permit an evaluation of the possible health consequences of herbicide exposure, and the Vietnam Experience study will give information regarding health risks that may be associated with the general (Army) service experience.

Unavoidable limitations of the proposed studies, or indeed any other studies which could be done, will preclude describing the results as "definitive." A number of limitations have already been mentioned, but some of them need to be repeated here, and a few more need to be added. An important limitation is that the proposed studies are observational, as opposed to experimental, and observational studies inherently require some tempering of the inferences drawn from them. Another general caveat is that it is not possible to prove a negative -- that is, it will never be possible to say with certainty that herbicide exposure or some other factor connected with Vietnam service did not cause any adverse health effects. In addition, when evaluating negative findings, the study power, or sensitivity, must always be kept in mind. The proposed studies will be quite powerful, but they will not provide answers to all health questions that might arise. However, if no increase in risks is found, these studies should be of substantial value in easing the concerns of veterans.

The ability to detect such specific increases will depend on the magnitude of the risk and the numbers of veterans (cases and controls in the Selected Cancers study) studied; the possibilities for exposure misclassification between the "likely exposed" and "likely not exposed" cohorts in the Agent Orange study have already been mentioned as a cause of concern. Moreover, even in the absence of exposure misclassification, the studies will have low power for rare diseases and/or low increases in risk, or for increases in risk limited to those veterans with prolonged and/or heavy exposure to herbicides or some other harmful factor. Thus, an overall finding of no increase in risk might "hide" a real increase for specific disease categories or special groups of veterans. But if the increase is limited to very rare categories of disease or to special veterans, then the study still has the utility of putting some boundary on the scope of the problem for most veterans.

The lack of strong hypotheses has been mentioned previously and this has led us to propose a rather wide ranging investigation. Thus, we may not give enough emphasis to some crucial factor. Our proposal to keep open the option of modifying our interviews and examinations mitigates this concern somewhat. However, it is conceivable that we will not include some critical item in our investigation, and from this type of omission there is no recovery.

Depending on the results of analysis, the design of the Agent Orange study may present unusual problems of inference. Some examples follow. If the first cohort ("likely exposed") appears to have significantly higher

disease risks than the second cohort ("likely not exposed") and the third cohort, then, depending on such considerations as the magnitude of the increase in risk, the inference will be clear -- herbicide exposure confers a health decrement. But suppose that the first and second cohort have similar disease risks and that they are both higher than the third. Then, one will be at a loss to say if the lack of difference between the first two and their similar difference with the third is due to exposure misclassification in the first two cohorts or to the difference in service experience.

Another problem of inference will be false positive findings. We plan to make comparisons of presumed herbicide exposure and/or Vietnam service for numerous health outcomes. There is, therefore, a certain probability that several of these will show statistically significant positive associations even if, in truth, there are none. It is difficult to a priori specify how these are to be handled. It may be that some such associations will be "convincing," in and of themselves, whereas others may not. Making such inferences transcends from the cold objectivity of statistics to the art of medicine -- at this stage considerations such as the biological plausibility of associations play a large part. In addition, the following approach may help in making such judgments. If the number of significant associations found is reasonably close to the number expected under the null hypothesis (e.g., 5% significant if working at an alpha = 5% level) and if the associations are relatively well balanced with respect to the direction of the association (e.g., if the number of instances where presumed herbicide exposure and/or Vietnam service appears harmful is approximately the same as where service appears protective), then we might be inclined to attribute the significant findings to chance. Finally, it is not unlikely that we will be left with equivocal positive results.

6. Report of Study Findings

CDC will prepare comprehensive reports of the findings for each of the study phases. The credibility of the results will be enhanced if the major findings are released simultaneously in peer-reviewed medical journals.

7. Timetable, Milestones, and Reports

Month 1 in the following timetable is December 1983. The timetable is ambitious and may be difficult to follow. CDC will do its utmost to ensure that there are no avoidable delays. It is projected that the Selected Cancers study will be finished last, at Month 69. The rate limiting factor for this study is the relatively low number of cases that will accrue each year. If CDC can identify other population-based cancer registries that have good case-ascertainment rates and that are willing to participate, the completion date would be sooner than the date currently projected.

Month Number	Major Milestone
1	- begin selecting Vietnam Experience (VE) main study subjects
4	- obtain OMB approval
7	- Random Digit Dialing Contract Award
	- Selected Cancers (SC) Data Collection Agencies Contract Award
9	- Agent Orange (AO)-VE Interview Contract Award
	- begin interviews, AO and VE pilot studies
10	- SC interviews begin
	- SC Pathology Contract Awards
11	- Examinations Contract Award(s)
12	- Company location for first 25 battalions complete, AO study
13	- VE study main interviews begin
14	- assess AO and VE pilot study
16	- begin VE study medical exams
	- begin selecting AO main study subjects
17	- selection of VE study individuals complete
18	- company location for second 25 battalions complete, AO study
23	- complete VE study mortality data collection
29	- report VE study mortality data
30	- complete VE study interviews
33	- complete VE study medical exams
39	- report VE study interview data
42	- report VE examination data
45	- complete AO study interviews
49	- report AO study mortality data
52	- complete AO medical exams
	- report AO study interview data
58	- report AO study exam data
63	- complete SC study histological review
69	- report SC study data

8. Investigators

These studies will be conducted under the direction of staff assigned to the Agent Orange Projects, an organizational entity located in the Chronic Diseases Division of CDC's Center for Environmental Health; oversight of laboratory work will be by the Clinical Chemistry Division, also of CDC's Center for Environmental Health.

The following staff, drawn from CDC's Agent Orange Projects group and Cancer Branch, have contributed to the scientific development of this protocol: Lee Annest, PhD; Edward Brann, MD, MPH; Pamela Byrnes; Pierre Decouflé, ScD; J. David Erickson, DDS, MPH, PhD; Nancy V. Hicks, RN, MS; Michael Kafrissen, MD, MPH; Peter M. Layde, MD, MSc; Maurice LeVois; Marion R. Nadel, PhD, MPH; Thomas K. Welty, MD; Matthew M. Zack, MD, MPH. Robert Diefenbach, John Gallagher, Peter McCumiskey, Melvin Ralston, and Joseph Smith have provided technical and administrative support, and secretarial assistance has been given by Gerri Culpepper, Teresa Ellington, Janiece Myers, Emily Peters, Jean Reynolds, Hazel Riley, and Effie Spencer. The staff of the Army Agent Orange Task Force, under the direction of Richard C. Christian, has given valued advice.

9. Protocol Review; Study Oversight

A draft of this protocol received wide scientific review. A panel of CDC scientists from programs outside of the division responsible for the studies conducted a scientific evaluation. The Office of Technology Assessment, the Science Panel of the Agent Orange Working Group, and the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants also conducted scientific reviews. In addition, CDC transmitted copies of the draft protocol to the representatives of about 15 veterans' organizations for their consideration. This version of the protocol incorporates a number of changes suggested during these reviews. The written reviews received, and CDC's responses to them, are available on request. Since the detailed interview instruments and examination protocols are currently being developed, CDC will make these available on request to interested parties when they are completed. This version will receive "human subjects review" by CDC's Institutional Review Board and review by the Office of Management and Budget.

CDC will conduct the studies with guidance from a steering committee. It has been requested that a subcommittee of the panel which provides oversight of the Ranch Hand studies be formed for this purpose. CDC proposes that steering committee meetings be held at 6-month intervals, to be supplemented by other meetings as the need arises.

Table 1

Cumulative Expected Numbers of Deaths by Cause[1] in a Hypothetical Cohort of 6,000 Men Aged 22 in 1968 and Followed Through 1984 (17 Years)

Cause of death[2]	Expected Number of Deaths
All causes	213.0
Accidents (E800-E949)	79.1
Motor vehicle (E810-E823)	48.3
Other (E800-E807, E825-E949)	30.8
Suicide (E950-E959)	25.5
Homicide (E960-E978)	27.3
Diseases of Heart (390-398, 402, 410-429)	18.6
Malignant Neoplasms (140-204)	17.3
Cirrhosis of liver (571)	6.6
Cerebrovascular diseases (430-438)	3.6
Influenza and Pneumonia (470-474, 480-486)	2.9
Diabetes Mellitus (250)	2.1
Nephritis and nephrosis (580-584)	0.7
Bronchitis, emphysema and Asthma (490-493)	0.5
Septicemia (038)	0.5
All other causes (residual)	28.2

[1]Expected numbers based on 1978 U.S. age-specific rates for males. The age-specific rates were quinquennial (5 years), and the cumulative rates used to derive the expected numbers were computed by weighting the quinquennial rates by the number of years of cohort experience in each quinquennium (constant cohort size). Source of rates: Vital statistics of the U.S.:1978, Vol. II, Mortality Part A, NCHS, 1982.

[2]Numbers in parentheses are the relevant codes from the Eighth Revision International Classification of Diseases, Adapted.

Table 2

Power[1] to Detect Various Relative Risks
in the Agent Orange and Vietnam Experience Studies,
by Prevalence of Condition in "Unexposed" Group

A. Interview Phase (6,000 per group)

Prevalence per 100 of Condition in "Unexposed" Group	Relative Risk 2	4	6	8
0.10	0.321	0.928	0.998	0.999+
0.20	0.576	0.998	0.999+	
0.30	0.750	0.999+		
0.35	0.811			
0.40	0.859			
0.50	0.923			
1.00	0.997			
1.50	0.999+			

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

Table 2 (continued)

Power[1] to Detect Various Relative Risks
in the Agent Orange and Vietnam Experience Studies,
by Prevalence of Condition in "Unexposed" Group

B. Examination Phase (2,000 per group)

Prevalence per 100 of Condition in "Unexposed" Group	Relative Risk 2	4	6	8
0.10	0.108	0.475	0.778	0.923
0.20	0.218	0.794	0.975	0.998
0.30	0.321	0.930	0.998	0.999+
0.35	0.370	0.960	0.999	
0.40	0.416	0.978	0.999+	
0.50	0.502	0.994		
1.00	0.796	0.999+		
1.50	0.926			
2.00	0.976			
2.50	0.993			
3.00	0.998			

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

Table 3

Selected Health Outcomes Reported To Be Associated with Exposure to TCDD - Animal and Human Literature*

Dermatologic
- Chloracne
- Hirsutism
- Hyperpigmentation

Hepatic
- Porphyria cutanea tarda
- Hepatomegaly
- Elevated serum levels of hepatic enzymes

Neuropsychologic
- Peripheral neuropathy
- Asthenia and lethargy

Immunologic
- Impaired cutaneous delayed hypersensitivity response
- Increased risk of infection

Reproductive
- Reduced fecundity
- Adverse pregnancy outcomes

Cancer
- Soft tissue sarcoma, lymphoma, and nasopharyngeal and nasal

General
- Lipid metabolism: Hypercholesterolemia and hypertriglyceridemia

*This table is by no means an exhaustive list (see Appendix B for literature review). It is intended to show the wide range of health outcomes postulated to be linked to TCDD exposure.

Table 4

Estimated Prevalence of Vietnam Service and Expected Number of Cases of Cancer for the Selected Cancers Case-Control Study in Males Aged 30-54 in 1986 in the SEER Areas

Age	Number of Males[1]	Prevalence of Vietnam Service[2]	Estimated Yearly Number of Cases[3]			
			Soft Tissue[4] Sarcoma	Lymphoma[5]	Nasal and[6] Nasopharyngeal	Primary Liver
30-34	980	4.9	20	53	4	3
35-39	907	11.7	14	45	5	3
40-44	740	12.5	17	52	6	5
45-49	590	3.7	22	75	10	12
50-54	552	1.5	33	106	17	20
Total	3,769	7.4	106	331	42	43

1 Estimated number of males (thousands) in SEER areas, 1976 data projected to 1986, National Cancer Institute Monograph 57, 1981.

2 Percent of males who are Vietnam veterans; estimated from VA data on numbers of Vietnam era veterans and assumption that 32.2% of Vietnam era veterans served in Vietnam.

3 Incidence of cancers derived from National Cancer Institute Monograph 57, 1981.

4 Includes the following (morphology-based) tumor types: fibrosarcoma, malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, Kaposi's sarcoma (estimate based on pre-AIDS incidence), blood vessel sarcoma, nerve sheath sarcoma, synovial sarcoma, malignant mesenchymoma, malignant paragarglioma. Incidence estimates also based on categories "sarcoma NOS" and "other sarcoma."

5 Includes Hodgkin's Disease and non-Hodgkin's lymphoma.

6 Includes the following topographic tumor types: nasopharynx, nasal cavity, accessory sinuses.

7 Includes liver and intrahepatic bile ducts.

Table 5
Power[1] of Selected Cancers Case-Control Study
to Detect Increased Relative Risks

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

Study Year 1

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

Study Year 2

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

Study Year 4

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

Study Year 4

	Number[2]	Control Group Prevalence of Vietnam Veterans 0.050	0.075	0.100
Soft Tissue Sarcoma	425	0.92	0.98	0.99+
Lymphoma	1,324	0.99+	0.99+	0.99+
Nasal & Nasopharyngeal	170	0.70	0.82	0.89
Liver	170	0.70	0.82	0.89
Controls	1,300			

Table 5 (continued)

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

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

Type of Participant	Number[2]	Possible Prevalence of Agent Orange Exposure Among Vietnam Veterans 0.10	0.25	0.50
Soft Tissue Sarcoma	425	0.33	0.62	0.85
Lymphoma	1,324	0.49	0.85	0.99
Nasal & Nasopharyngeal	170	0.23	0.41	0.61
Liver	170	0.23	0.41	0.61
Controls	1,300			

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

Type of Participant	Number[2]	Possible Prevalence of Agent Orange Exposure Among Vietnam Veterans 0.10	0.25	0.50
Soft Tissue Sarcoma	425	0.96	0.99+	0.99+
Lymphoma	1,324	0.99+	0.99+	0.99+
Nasal & Nasopharyngeal	170	0.81	0.98	0.99+
Liver	170	0.81	0.98	0.99+
Controls	1,300			

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

2 Estimated number of participants

APPENDIX A
(November 1982)

Protocol Outline
Tentative Timetable
Epidemiological Studies of the Health of Vietnam-Era Veterans (Agent Orange)

Overall Design

The Centers for Disease Control (CDC) recommends two complementary historical or retrospective cohort studies. One study will compare the health of a group of U.S. veterans of the Vietnam conflict with the health of a group of Vietnam-era veterans who did not serve in Vietnam; it may include individuals from all four branches of the military. The purpose of this study will be to make an assessment of the possible health effects of the general Vietnam service experience. The other study, which is designed to evaluate the health effects of possible exposure to herbicide Agent Orange, will compare the health of three groups or cohorts of Vietnam veterans who differ in their probable level of exposure to Agent Orange. This second study will focus primarily on veterans of the Army but will probably include veterans of the Marine Corps.

Each of these two studies will have three major components: 1) a mortality assessment (mortality followup will be repeated every 5 years for the foreseeable future); 2) a health and exposure questionnaire; and 3) a clinical and laboratory assessment. The studies will have several other features in common. However, the sampling plans and some of the health outcomes measured in the questionnaire and clinical assessments will differ between the two studies. Moreover, they will follow different timetables. They are designed to answer related but distinct questions of importance to Vietnam veterans and their families.

These two studies should be sufficient to meet the directive of Congress which instructed the Veterans Administration to conduct an "epidemiological study"; in addition, they are responsive to current veterans' and congressional concern. However, these studies are but a part of the Federal effort to provide answers about the possible health effects of herbicides and their contaminants, and about the effects of military service in Vietnam. Other major Federal activities include: 1) CDC's ongoing study which is designed to determine if Vietnam veterans are at increased risk of fathering babies with birth defects; 2) CDC's NIOSH Dioxin Registry, which will assess the health effects of occupational exposure to dioxin during the manufacture of herbicides and related chemicals; 3) the U.S. Air Force's comprehensive health study of veterans who applied herbicides in Vietnam from fixed-wing aircraft ("Ranch Hand" study); 4) the Veterans Administration's (VA) proportionate mortality study of Vietnam veterans; the VA is also supporting protocol development for a study of twins, one of whom went to Vietnam and one of whom did not.

Composition of Cohorts and Sampling Plans

The choice of individuals for inclusion in the various study cohorts will derive from review of military records from the Vietnam era. Considerable thought about and work with records from Vietnam has been done by the

Department of Defense (primarily staff of the Army Agent Orange Task Force--AAOTF), the Veterans Administration, and the White House Agent Orange Working Group. A consensus seems to have been reached that the choice of individual veterans for an Agent Orange study will involve the use of personnel records and company level action records and a variety of herbicide usage records. More thought needs to given to the specific organization and analyses of records which might be used for a Vietnam Experience study, but it is recommended that company level records also be used for this study.

a) Agent Orange Study

A good design for a historical cohort study of the possible health effects of Agent Orange would involve the use of 2 groups of men who were as similar as possible in all respects except for their exposure to the herbicide. One group would ideally be free from all exposure while the others would have been subjected to "meaningful" exposure. (Other attractive designs might include subdivisions of those exposed based on levels and/or duration of exposure, or even continuous measures of exposure for individual veterans.)

It appears that such an ideal is not attainable. Obstacles include: 1) the military records which must be used were made during a war and, therefore, of uneven quality; 2) an inability to define objectively "meaningful" exposure; 3) the difficulty in ensuring that veterans who were possibly or likely exposed (by whatever measure) are comparable (with respect to all things which might influence health) to veterans who were not exposed. Under ordinary circumstances, such obstacles would probably prevent the initiation of an Agent Orange study. It is, therefore, mandatory that advance advice and consent be obtained from veterans' groups with respect to study policies and procedures, especially those directed at defining Agent Orange exposure.

The important company records which give information about troops are the morning reports and the journal files. The morning reports can be used to document the presence or absence of individual servicemen on a daily basis while the daily journal files will indicate the locations of companies in time and space. The major herbicide records are those which document the time and location of fixed-wing aircraft applications of herbicide (Ranch Hand missions--contained on the "Herbs" tape), base perimeter applications records, and information about Ranch Hand mission aborts (dumps). The choice of an individual for inclusion in the "likely-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 chosen because of a measure of their company's distance in time and space from any herbicide applications.

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. 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 "exposed" to Agent Orange are comparable to "non-exposed" troops with respect to other factors which might influence health is another issue which 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 and differed in terrain and flora from those 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 much of the recent thinking about the subdivision of troops into "exposed" and "non-exposed" groups has been directed at choosing the 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 are truly "exposed" into the "non-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 (and time during the war) but will differ in regard to their exposure likelihood. These two cohorts will be comparable but suffer from imprecision of exposure separation. The third cohort will be drawn from another area of Vietnam (but from the same time period), an area where there is good evidence of little or no herbicide usage. This cohort will give maximum exposure separation from the "exposed" cohort but may suffer from a lack of comparability in respect of other health-influencing factors. This design is incomplete, as is illustrated in the following 2 x 2 table which cross-classifies exposure by a measure of general experience, which will be called "combat."

		Agent Orange Exposure	
		Yes	No
"Combat"	Yes	Cohort 1	Cohort 2
	No		Cohort 3

The empty cell, representing the combination of Agent Orange exposure with no "combat," cannot be filled, because it is our understanding from the military that Agent Orange use was inextricably entwined with a certain "combat" experience. Because of its incompleteness, 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 based on an approach which 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, currently being conducted by the U.S. Air Force, may help in the interpretation of this incomplete design. The Ranch Hand study will compare the health of crews who flew the herbicide spray missions with air crews who did not fly spray missions. Thus, it will provide information about Agent Orange exposure in the absence of the general experience of ground troops.

b) Vietnam Experience Study

The idea of studying ill-health effects which might derive from the "general experience" of having been in Vietnam is at once attractive and unappealing. It is attractive because there may have been many factors which could have adversely affected those who served in Vietnam, in contrast to their counterparts who served elsewhere. And 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 many factors, many of which are unknown, poorly defined, or not quantifiable. Nevertheless, it is our opinion that this is an important question to the Vietnam veteran, and one which deserves as much attention as the issue of the possible effects of Agent Orange.

Viewed in the broadest terms, the Vietnam "experience" could have influenced anyone who served there. It is, therefore, suggested that consideration be given to the inclusion of veterans of the Army, Navy, Marines, and, if possible, the Air Force (the records systems of the Air Force might make inclusion of that service's veterans very difficult).

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 feel that such factors would have existed for all Vietnam veterans. Specifically, it is their belief that being sent to Vietnam was a matter of the "luck of the draw" for those who were drafted or who were short-term enlistees. Serving in Vietnam, the U.S., in Europe, or elsewhere was, in their opinion, a matter which depended on occupational specialty and the operational needs of the various commands. Thus,

any given serviceman was at risk of serving anywhere where there was a need for his occupational specialty.

Choice of individuals for the two cohorts of this study should be made after a review of company and personnel files in much the same manner as will be done for the Agent Orange study. A simple random sample or a stratified random sample of Vietnam veterans and non-Vietnam veterans would probably be the method of choice but the filing of the available records probably makes this infeasible. Therefore, we recommend a cluster sampling of military units (much as will be done for the Agent Orange study) and a random sampling within clusters as the method for selecting members of each cohort.

Sample Sizes

It is recommended that each of the 5 cohorts (3 Agent Orange study and 2 Vietnam Experience) be composed of 6,000 servicemen. All of these individuals will be included in the mortality studies, and it is hoped that up to 90% of the surviving cohort members will be included in the questionnaire phase of the studies. (The results of the Ranch Hand study, better than 95% interview completion, give reason to set such an optimistic goal. If, however, the questionnaire pilot studies give indications of completion rates much under 70 or 75%, careful consideration should be given to not proceeding with the main studies.) The number of 6,000 for each cohort was chosen because comparisons between 2 groups of between 5,000 and 6,000 each will be able to detect (alpha = beta = 0.05, 1-tail) 2-fold increases in the relative risk for health outcomes which ordinarily occur at the rate of 0.5%, for example, all cancers (detecting associations for specific cancers would require truly massive cohorts--this problem is probably best approached through specific case-control studies).

For the clinical and laboratory phases, it is suggested that random samples of 2,000 from each cohort be chosen. It is hoped that as many as 80% of those chosen will participate and, as with the questionnaire phases, if the pilot study shows rates much below the 70% level, it will be necessary to question the wisdom of proceeding with the main study phases. The number 2,000 was chosen because samples between 1,500 and 2,000 will give good power (alpha = beta = 0.05, 1-tail) to detect 2.5-fold increases in the risk of outcomes which usually occur at the rate of 1.0%.

(The major health outcome categories from which the questionnaire and clinical laboratory phases will be developed during protocol design and review are listed in a later section of this outline.)

Study Sequences

Three phases are planned for each of the 2 studies and each phase will culminate in a separate report. The 3 reports will concern 1) mortality experience of the cohort members; this phase of the study will also give an indication of the proportion institutionalized, 2) the results of the health questionnaire, and 3) the results of the clinical and laboratory tests. It is anticipated that work will proceed first on the Vietnam Experience study because there will be less work involved in selecting the cohort members than there will be for the Agent Orange study. Within each study, ascertainment of

vital status will be a part of the process of locating cohort members for the health questionnaire and clinical/laboratory phases. Thus, mortality analysis will be completed first; reports on the health questionnaire and clinical/laboratory analyses will follow later. Even though these studies are subdivided into phases, it is expected that at some point in time work will be proceeding simultaneously on both studies (see schedule, later in this outline).

The major steps which will be required to complete the two studies are (after full protocol design and approval and after pilot testing of procedures):

1) Selection of individual cohort members by the Army Agent Orange Task Force (AAOTF)

   For the Vietnam Experience study, identifying information about the cohort members will be transmitted to CDC immediately after selection. For the Agent Orange study much more work will be required of AAOTF personnel because of the need to review exposure information. Identifying information about cohort members for each study will arrive at CDC in small batches, possibly on a monthly basis, as they are selected. Therefore, the selection will be done in such a way that an appropriate balance of "exposed" and "non-exposed" for the Agent Orange study and of Vietnam and non-Vietnam veterans for the Vietnam Experience study are included in each batch.

2) Vital Status Determination and Location of Cohort Members

   As soon as a batch of information for study individuals is received, a check will be made against the Beneficiaries Identification and Records Location System (BIRLS) files and the National Death Index to try to ascertain those individuals who are deceased. For those who are found to be dead, collection of death certificates, pathology reports and other relevant material will ensue. Procedures to determine the location of those currently alive will begin simultaneous with the checks against the BIRLS and National Death Index--the first step will be to check against Internal Revenue Service (IRS) files, which is a rapid and inexpensive method to obtain relatively current addresses for taxpayers. For those individuals who are not found on the BIRLS file or National Death Index and who are also not found on the IRS files, more expensive and time consuming methods of location will be used. The goal for both studies will be a location rate of 95% for those who are presumed alive.

3) Health Questionnaire

   Interviews of about 45 minutes in length will be conducted by telephone where possible. For potential respondents without telephones, personal interviews will be conducted at a place convenient for the respondent; for potential respondents who are institutionalized, personal interviews will be conducted at the place of institutionalization. The major outcomes from which questionnaire items will be chosen during the stage of full protocol development

are listed later in this outline. The goal for both studies will be an interview completion rate of better than 90% of those located.

4) Clinical and Laboratory Examinations

Clinical examinations of the 2,000 individuals from each of the 5 cohorts will take place at 1 or 2 examining facilities, much like that used by the Ranch Hand study. The physical examination will include a standard, good quality review of systems. Multiple laboratories may be used for the various laboratory tests, but each particular test will be performed in a single laboratory. Special emphasis will be given to the clinical and laboratory outcomes which will be chosen during protocol development from among those which are listed later in this outline.

Vietnam Experience Study
Tentative Timetable

This tentative timetable is divided into 2 phases - protocol development and study implementation. However, some tasks which are formally a part of the implementation phase are scheduled to begin during the development phase. This approach is proposed so that there will be no unnecessary delays in the event that the protocol review goes smoothly and according to schedule. Month number 1 for each study phase begins at the time resources are made available to CDC by the VA.

Study Phase	Month Number		Major Milestones
Protocol Development	1	o	recruit new personnel and short-term consultants for protocol development
	2		
	3	o	complete development of protocol
	4	o	complete peer review of protocol
		o	complete preliminary work with military files for sample selection
		o	begin developmental work for contracts for questionnaire administration, clinical and laboratory work
	6	o	complete OMB review
		o	complete selection of pilot study samples
Study Implementation	1	o	begin selection of main study samples
		o	begin final formatting of questionnaires and clinical instruments
	2	o	begin data collection for main study mortality analysis
	6	o	award contract for questionnaire administration

Vietnam Experience Study
Tentative Timetable (continued)

Study Phase	Month Number		Major Milestones
	7	o	begin questionnaire pilot study
	10	o	award contract for clinical and laboratory studies
	11	o	begin clinical and laboratory pilot study
		o	evaluate questionnaire pilot study
	12	o	begin questionnaire main study
	16	o	evaluate clinical and laboratory pilot study
	17	o	begin clinical and laboratory main study
	23	o	complete study sample selection
	32	o	complete mortality study data collection
	35	o	REPORT mortality study analysis
	36	o	complete questionnaire data collection
	41	o	complete clinical and laboratory data collection
	42	o	REPORT questionnaire analysis
	47	o	REPORT clinical and laboratory data collection

Agent Orange Study
Tentative Timetable

Timetable for this study will parallel the Vietnam experience study timetable in the early phases (i.e., protocol development and review). Because of the extra time required to review military records for determination of Agent Orange exposure, data collection for the 3 study phases (mortality, questionnaire, clinical) will begin approximately 6 months after the comparable phase of the Vietnam experience study. Accordingly, the reports will appear 6 months later:

Study Phase	Month Number	Major Milestones
Study Implementation	41	o REPORT mortality study analysis
	48	o REPORT questionnaire analysis
	53	o REPORT clinical and laboratory data collection

Tentative List of Items for Health Questionnaire, Physical Examination and Laboratory Analysis

The questionnaire and physical examination instruments will be drawn up during the protocol development phase. The following is a list of important elements which will serve as the starting point for development of the final instruments.

Questionnaire Information:

1. Locator and Tracing Information

2. Demographic Information

3. Other Potential Confounders:
   - Military History:
     - Drafted vs enlisted status
     - Military occupational specialty
     - Combat vs noncombat experience: Duties, places, dates
       - (develop combat index from casualty rates, # enemy attacks, etc., from sample of records as well as asking men)
     - Area of service
     - Discharge status
   - Tobacco (types of use, amount of use, dates of use)
   - Alcohol (types of use, amount of use, dates of use)
   - Medications (amount of use, dates of use):

3. (Continued)
   Antimalarials--primaquine, chloroquine, fansidar, dapsone, etc.
   Antifungals--griseofulvin, etc.
   Other medications (also include reason for use)
Illicit drug use (amount of use, dates of use):
   Marijuana, barbiturates, amphetamines, opiates, cocaine, PCP, hallucinogens
Specific chemical exposures (how, how much, and when exposed; CF.):
   Agent Orange--include 2,4-D and 2,4,5-T
   Other herbicides
   Pesticides, insect repellants
   Riot control agents
Occupational history (type of job, dates, chemical exposures, if any)
Hobbies (e.g., chemical exposures, risk-taking behaviors)
Habits: L. Breslow's healthy habits, index of social linkage

4. Medical history:
Family history:
   Immediate family: age now or at death; if dead, cause of death; Illnesses requiring hospitalization, surgery, or medication
Personal history (before, during, and after military service):
   Personal physician: name, address, telephone number
   Specific illnesses (who, what specifically, when, how severe, source of verification):
      high blood pressure, heart disease, cancer, stroke, lung disease, diabetes, mental or nervous diseases, liver disease, arthritis, repeated infections, malaria, parasitic diseases
   Hospitalizations (reason, year, duration, source for verification)
   Surgical procedures (reason, year, duration, source for verification)
   Blood transfusions (reason, year, source for verification)
   Injuries (year, severity, source for verification)
   Allergies (year, severity, source for verification): asthma, rash, hay fever, medication reactions
   Time lost from work _1 week (reason, year, duration, source for verification)
Review of systems: (date, duration, severity when positive response)
   Weight on discharge from military, 1 year ago, and today
   General: change in weight (if loss, intentional or unintentional), loss of appetite, weakness
   Head: headaches, change in hair pattern
   Eyes: change in vision, irritated eyes
   Ears: change in hearing, ear noises, ear infections
   Nose: sinus infections, nosebleeds
   Mouth: sore tongue, sore throat
   Neck: swollen glands, goiter (large thyroid), stiffness, pain
   Chest: shortness of breath, cough, wheezing, phlegm, chest pain, heart attack, heart failure, heart murmur, palpitations
   Abdomen: difficulty swallowing, vomiting, gallstones, difficulties with digestion, change in bowel habits, blood in bowel movement, hemorrhoids, hernia

4. (Continued)

Genitourinary: venereal diseases, kidney stones, kidney infections, blood in urine, impotence, decreased sex drive, infertility, children with birth defects

Limbs: swelling, change in skin color, joint pain, difficulty with movement, difficulty with coordination, numbness, tingling, pains

Neuropsychiatric: concussion, forgetfulness, sleep disorders, paralysis, seizures, dizziness, depression

Skin: rashes, boils, acne, scars, sunburns easily, bruises easily

5. Physical examination (CF., NCHS and Ranch Hand physical exam sheets):

General: appearance, weight, height, blood pressure, pulse, respiratory rate

Head: movements, hair pattern

Eyes: movements, conjunctivitis

Ears: hearing, infections

Nose: polyps, sinusitis

Mouth: teeth, tonsils, tongue, cheeks, throat

Neck: movement; thyroid enlargement, nodules, tenderness; parotid enlargement or tenderness; cervical lymphadenopathy

Chest: movements, bony abnormalities, axillary lymphadenopathy

Lungs: rales, rhonchi, wheezes, dullness, hyperresonance

Heart: extra sounds, murmurs, rubs, size

Abdomen: liver size, spleen size, tenderness (location), masses, hernia, testicular masses, inguinal lymphadenopathy, rectal exam,

Back: scoliosis, kyphosis, tenderness (location)

Limbs: movements, edema, arthritis, varicose veins, nail clubbing, peripheral pulses

The following exams should be done by a dermatologist and a neurologist, respectively:

Skin: rash, scars, ulcers, acne, masses, spider angiomata, etc.;

Neurological exam:

Mental status:

Emotional responses:

Cranial nerves:

Motor systems: gait, movement, tremors, muscle bulk, muscle tenderness

Reflexes:

Sensory tests:

6. Psychological testing (CF., Ranch Hand set of tests--need consultation):

Minnesota Multiphasic Personality Inventory

Wechsler Adult Intelligence Scale

Reading Subtest of Wide Range Achievement test

Halstead-Reitan Neuropsychological Test Batteries

Wechsler Memory Scale

Cornell Index

7. Laboratory tests:

Blood:

Complete blood count: hematocrit, hemoglobin, red cell count, white cell count and differential, platelet count

Liver function tests: SGPT, GGTP, total protein, albumen (SGOT, bilirubin, and alkaline phosphatase not necessary but may occur on SMA-12)

Kidney function tests: BUN, creatinine

Lipid function tests: total and HDL cholesterol, fasting triglycerides

Hepatitis B surface and core antigens

Immunoglobulin quantitation: IGG, IGM, IGA, IGE, IGD

Two hour post-prandial blood glucose

VDRL

Free T4 and T3 uptake

Serum stored for serological testinG (CF., Ranch Hand positives, melioidosis)

Urine:

Urinalysis: microscopic and dipstick (protein, glucose, hemoglobin)

Urine total porphyrins and porphyrin profile

Stool:

Qualitative test for blood (during physical exam)

Other tests depending on results from Ranch Hand study:

Chest X-ray

Electrocardiogram

B- and T-lymphocyte quantitation

APPENDIX B

Literature Review

1. Health Effects of Herbicides and Dioxin

1.1. Dermatologic Effects

Chloracne is a refractory skin disease characterized by inclusion cysts, comedones, and pustules, with eventual scarring of the skin, produced by environmental exposure to certain halogenated aromatic compounds in humans (Taylor, 1979). A similar condition is also seen in animals. TCDD is an active skin irritant and produces local lesions resembling human chloracne in the skin of rabbit ears (Kimmig and Schulz, 1957). An analogous hyperkeratosis and modulation of sebaceous structures to keratin cysts was observed in monkeys and hairless mice. Since in these species the skin areas affected by TCDD all lack major hair growth, and, in men, lesions usually do not occur in the follicles of beard hair, it has been suggested that the hair shafts on the unaffected portions of the body may facilitate drainage of sebum and keratinaceous debris (Greig, 1979). After acute exposure to TCDD, blepharitis, loss of fingernails and eyelashes, and facial alopecia were observed in monkeys (McConnell et al., 1978a). Horses accidentally exposed to salvage oil containing TCDD in Missouri had hyperkeratotic skin lesions and hair loss, and dogs, cats, and mice similarly exposed had ulcerative dermatitis and hair loss (Case and Coffman, 1973; Carter et al., 1975).

In humans, chloracne is the most frequent and consistent acute health outcome of exposure to TCDD. It is often observed in exposed individuals who have no other apparent health effects. However, since it is usual that only patients with chloracne are studied further, it is not possible to accurately estimate the relative frequency of other adverse effects of exposure. There are, however, reports of individuals without chloracne who developed other acute symptoms possibly related to TCDD exposure (Jirasek et al., 1973; Oliver, 1975).

Cases of chloracne were reported after the explosions which occurred at factories in Nitro, West Virginia, in 1949 (Suskind, 1978), in Ludwigshafen, West Germany, in 1953 (Goldmann, 1972, 1973), in the Netherlands in 1963 (Dalderup, 1974; Hay, 1976), in Grenoble, France, in 1966 (Dugois et al., 1968), and in the United Kingdom in 1968 (May, 1973). Chloracne has also been reported in occupational exposures that did not involve explosions. These were reported from factories in Middle Rhein, West Germany (Bauer et al., 1961), Hamburg, West Germany (Kimmig and Schulz, 1957; Schulz, 1957), Grenoble, France (Dugois et al., 1958), Newark, New Jersey (Bleiberg et al., 1964), the U.S.S.R. (Telegina and Bikbulatova, 1970), and Czechoslovakia (Jirasek et al., 1973). In addition to these industrial exposures, chloracne developed in two government scientists involved in the experimental preparation of TCDD (Oliver, 1975). In 1976, the explosion at the ICMESA factory near Seveso, Italy, resulted in the contamination of a large, densely populated area; 187 cases of chloracne have been reported, mostly in children (Malizia et al., 1979). A few of the individuals exposed to the TCDD-contaminated horse arenas in Missouri may have had chloracne (Carter et al., 1975; Kimbrough et al., 1977).

Chloracne may persist for many years. For example, 14 of 122 persons with chloracne following the Nitro accident had lesions evident 28 years later (Crow, 1980). One case remained 18 years after the explosion in Ludwigshafen (Goldmann, 1972). Thirteen years after the explosion in Amsterdam, 10 of 50 original cases remained (Hay, 1976). Of 41 employees surveyed 10 years after the U.K. accident, 22 still had mild chloracne (May, 1982). A followup of 55 subjects with chloracne who had worked in the Czech factory revealed that 15% still had florid manifestations after 10 years (Pazderova-Vejlupkova et al., 1981).

Hyperpigmentation and hirsutism may accompany chloracne. Many of the Newark workers with chloracne also developed hyperpigmentation of the sun-exposed areas of the head, neck, and hands or hirsutism, which was always located on the temples. The severity of these conditions paralleled that of chloracne (Bleiberg et al., 1964; Poland et al., 1971). About one-quarter of the Czech workers with chloracne had either hyperpigmentation or hirsutism of the face or both (Jirasek et al., 1973). Mucous membrane irritation has also been reported in several groups of workers (Schulz, 1957; Poland et al., 1971; Goldmann, 1972).

1.2. Hepatic Effects

Hepatic porphyria, a disorder of heme pigment metabolism, can either be inherited or acquired by exposure, in both experimental animals and humans to certain polyhalogenated aromatic compounds, medications, and other environmental factors such as excessive alcohol consumption (Strik, 1979; Kimbrough, 1980). All of these chemicals inhibit uroporphyrinogen decarboxylase in the liver, but not in red blood cells. Porphyria cutanea tarda (PCT) is the most severe form of this type of porphyria. A diagnostic indicator of PCT is the simultaneous increase of both uro- and heptacarboxylic porphyrin in urine. It has been found that chronic hepatic porphyria without clinical symptoms begins with accumulation of these porphyrins in the liver, followed by their gradually increasing excretion in the urine. In PCT, skin findings are often associated with increased porphyrin excretion and include excessive skin fragility, vesiculobullous lesions on sun-exposed areas, hirsutism, and hyperpigmentation. However, it appears that PCT and chloracne are independent syndromes (Poland et al., 1971). Porphyria was observed after exposure to TCDD in rats, mice, and chick embryo cells (Goldstein et al., 1973; Kociba et al., 1976; Sinclair and Granick, 1974). It has also developed in several groups of exposed workers. Eleven of 29 Newark workers with chloracne had abnormal excretion of urinary uroporphyrins; of these, three had definite cases of PCT (Bleiberg et al., 1964). A re-examination of the same plant 6 years later revealed no clinical PCT and only one employee with mild persistent uroporphyrinuria (Poland et al., 1971). At least 11 cases of PCT were reported among Czech workers (Jirasek et al., 1973, 1974).

Other hepatic effects of TCDD include structural alterations, changes in serum enzyme levels, and changes in the biliary system, in a number of animal species (IARC, 1977; VA, 1981). Many of the reports of human exposures also mention hepatic effects (see also section on carcinogenicity, below). Liver damage was reported in workers in the factories in Hamburg, West Germany, Grenoble, France, Czechoslovakia, and the U.S.S.R. (Kimmig and Schulz, 1957; Dugois et al., 1958; Jirasek et al., 1974; Telegina and Bikbulatova, 1970). Three workers in Middle Rhein, West Germany, had morphological changes in

liver biopsies taken 5 years after their exposure ended (Bauer et al., 1961). Liver enlargement and tenderness were reported after the Nitro explosion, and liver damage and hepatitis were reported after the explosion in Ludwigshafen (Zack and Suskind, 1980; Goldmann, 1972). Hepatomegaly was reported among residents of the contaminated region of Seveso (Pocchiari et al., 1979).

Effects on enzyme levels have also been reported in humans. TCDD is known to be a potent inducer of a number of hepatic microsomal enzymes (Huff et al., 1980). Increased levels of urinary d-glucaric acid, an indirect measure of hepatic microsomal enzyme activity, were found in children living in the Seveso area (Ideo et al., 1982). Altered levels of other enzymes, mainly transaminases and gamma-glutamyl transferases, were also noted (Pocchiari et al., 1979). A slight elevation in the levels of urinary d-glucaric acid and gamma-glutamyl transpeptidase were also observed in a 10-year survey of U.K. workers (May, 1982). Slightly increased elimination of delta-amino levulinic acid has also been reported (Jirasek et al., 1974; Poland et al., 1971).

1.3. Neurological/Psychological Effects

Neurological effects of exposure to 2,4-D have been observed in both experimental animals and man. Myotonia of skeletal muscles was produced by 2,4-D administration to rats, guinea pigs, dogs, and rabbits (Danon et al., 1978; Eberstein and Goodgold, 1979; Drill and Hiratzka, 1953; Hill and Carlisle, 1947). Symptoms of asthenia, lethargy, and ataxia were observed in pigs, calves, rats, and mice (Hill and Carlisle, 1947; Bjorklund and Erne, 1966). Irregularities of EEG pattern have been observed in rats, cats, and dogs as well as demyelinization of the spinal cord (Desi et al., 1962).

In humans a number of case reports have described symptoms of peripheral neuropathy following poisoning by 2,4-D herbicides. Typical symptoms observed included asthenia, hypesthesia, and myotonia in the muscles of the extremities, hyporeflexia, and general muscular weakness leading to ataxia. Decreased nerve conduction velocities were measured in some cases (Goldstein et al., 1959; Berkley and Magee, 1963; Wallis et al., 1970; and see VA literature review). Irregularities in EEG patterns were observed in farmers exposed to 2,4-D (Kontek et al., 1973). In a survey of 292 workers in a factory that produced 2,4-D, reports of weakness, fatigue, and headaches were very common (Bashirov, 1969).

Neuropsychological effects were reported after most of the human exposures to TCDD. Typical complaints among factory workers included fatigue, headaches, weakness and pain, especially in the extremities, sexual dysfunction, loss of appetite, and irritability (Jirasek et al., 1973; Poland et al., 1971; Baader and Bauer, 1951; Goldmann, 1972; Bauer et al., 1961; Kimmig and Schulz, 1957; Crow, 1980; Dugois et al., 1958; Telegina and Bikbulatova, 1970). Two to three years following their exposure to TCDD, two laboratory scientists had similar complaints, including loss of energy and drive, irritability, visual problems, and diminished sense of taste (Oliver, 1975). Headaches were reported among people exposed to the contaminated horse arenas in Missouri (Carter et al., 1975; Kimbrough et al., 1977). Decreased auditory acuity and decreased sense of proprioception were noted among Newark workers. The Minnesota Multiphasic Personality Inventory (MMPI) was administered to the Newark workers. A significant positive correlation was

observed between the severity of active acne and the score on the hypomania scale of the MMPI (Poland et al., 1971). Abnormal EEG patterns were noted among workers in Czechoslovakia and Middle Rhein, West Germany (Jirasek et al., 1974; Bauer et al., 1961).

Neurological studies were conducted following the Seveso accident. A higher percentage of cases of idiopathic clinical or subclinical neuronal damage was found in the most highly contaminated zone than in zones with lower levels of contamination, for both adults and children. The most frequent pathological signs were detected in the peripheral nervous system. Signs of subclinical neuronal damage included reduced nerve conduction velocity (Boeri et al., 1978; Pocchiari et al., 1979). Altered nerve conduction velocity was more prevalent among exposed individuals with chloracne or increased levels of serum hepatic enzymes than among exposed individuals without these manifestations (Filippini et al., 1981). Of about 200 workers from the ICMESA plant and another factory in the same area who were examined for neurological function, 8 were diagnosed as having polyneuropathy of peripheral nerve fibers (Pocchiari et al., 1979). An increased prevalence of slowed nerve conduction velocities was observed among workers employed in the manufacture of 2,4,5-T and 2,4-D in Arkansas (Singer et al., 1982).

1.4. Immunological Effects

Acute and subacute doses of TCDD have produced atrophy of the thymus and other lymphoid tissues with loss of lymphocytes in monkeys, rats, mice, and guinea pigs (McConnell et al., 1978a & b; Vos and Moore, 1974). Changes in thymic weight appeared to be a very sensitive indicator of exposure to TCDD, since decreases in thymic weight occurred at doses which had no effect on body weight in rats, mice, and guinea pigs (Harris et al., 1973). Horses exposed to TCDD-contaminated salvage oil were found to have spleens reduced to one-third the normal size and small and inactive lymph nodes (Case and Coffman, 1973).

TCDD has also been shown to suppress immune function in animals, primarily thymic-dependent immune function. Suppression of mitogen responsiveness, skin-graft rejection, and delayed hypersensitivity responses have been observed (Vos and Moore, 1974; Vos et al., 1973; Faith and Moore, 1977). Suppression of these T-cell-dependent immune functions appears to occur without helper cell function being affected; thus, different functional subsets of T-cells seem to be selectively affected (Faith et al., 1978). Sensitivity to the immunosuppressive effect of TCDD appears to decrease with age. Exposure of the developing immune system during pre-, and/or post-natal life results in more severe effects than exposure during adult life (Vos and Moore, 1974; Luster et al., 1979). A slight suppression in humoral immunity has been noted (Vos et al., 1973).

Low doses of TCDD, which did not elicit clinical or pathological effects, did reduce host defenses in mice to Salmonella infection, while defense to pseudorabies virus was not affected (Thigpen et al., 1975). Susceptibility to Salmonella was found to result from increased sensitivity to bacterial endotoxin (Vos et al., 1978). Non-specific killing by macrophages or specific killing of Listeria was not impaired by TCDD treatment (Mantovani et al., 1979; Vos et al., 1978).

Reports of immunologic effects following human exposure to TCDD have been very rare. An increased susceptibility to infection was noted among workers following the Ludwigshafen accident (Goldmann, 1972). Following the explosion in Seveso, there did not appear to be an increase in number or severity of childhood infections, nor were results of immunological tests found to be abnormal (Reggiani, 1979, 1980; Malizia et al., 1979; Pocchiari et al., 1979).

1.5. Carcinogenic Effects

Several studies indicate that TCDD is carcinogenic in rodents, producing increased incidence of hepatocellular carcinomas and neoplasms in the lung, hard palate, nasal turbinates, and thyroid of the rat (Kociba et al., 1978; Toth et al., 1979; National Toxicology Program, 1982). Hepatocellular tumors, thyroid tumors, and fibrosarcoma of integumentary tissue have been produced in mice (National Toxicology Program, 1982a & b). TCDD may act as a promoter of liver tumors in the rat (Pitot et al., 1980).

An association between phenoxyherbicide exposure in forestry workers and soft tissue sarcoma has been noted in two Swedish case control studies as well as in the combined analysis of four American cohorts of workers industrially exposed to phenoxyherbicides (Coggon and Acheson, 1982; Editorial, 1981). Hardell and Sandstrom (1979) found a significant excess of malignant mesenchymal tumors in individuals occupationally exposed to phenoxyherbicide 10-20 years beforehand (relative risk 5.3, with 95% confidence limits 2.4-11.5). Eriksson et al. (1981) also found a significant association between exposure to phenoxyherbicides and soft tissue sarcoma (relative risk 6.8 with 95% confidence limits 2.6-17.3). The histologic distribution of tumor types in the exposed and unexposed groups was not recorded in either study.

Honchar and Halperin (1981) combined individuals from 4 cohorts industrially exposed to phenoxyherbicides and related compounds and found that 3 of 105 deaths had been due to soft tissue sarcoma compared with 0.07% of deaths in the total U.S. white male population aged 20-84. A fourth (recently deceased) case was subsequently reported in one of these cohorts (Cook, 1981). Additionally, three other individuals with soft tissue sarcomas were reported to have worked in 2,4,5-T production facilities (Moses and Selikoff, 1981; Johnson et al., 1981).

Other studies of workers exposed to phenoxyherbicides during their application have so far failed to confirm this association (e.g., Coggon and Acheson, 1982). However, in most cases the design of these investigations was such that only very high relative risks for soft tissue sarcoma were likely to be detected.

Hardell et al. (1981) found a significant excess of lymphomas in Swedish individuals occupationally exposed to phenoxyherbicides (relative risk 6.0, 95% confidence limits 3.7-9.7). The excess risk was similar for Hodgkin's and non-Hodgkin's lymphomas when analyzed separately. No other epidemiologic studies of this association have been reported. Compromised immunity is the strongest risk factor for development of lymphomas (Greene, 1982). Dioxins have immunosuppressant properties in animal species (see above), which presents an attractive hypothesis for the etiology of their postulated association with both soft tissue sarcoma and lymphomas.

At least two epidemiologic studies suggest a slight excess risk of stomach cancers in cohorts exposed to phenoxyherbicides and related compounds. Theiss et al. (1982) reported a significant excess of stomach cancers (3 observed vs. 0.6 expected) in 74 German workers who were exposed to trichlorophenol and dioxin 20 years before. Axelson et al. (1980) observed an apparent excess of stomach cancer (3 observed and 0.71 expected) among 348 railroad workers exposed to phenoxyherbicides and amitrol.

Hardell et al. (1982) reported that exposure to phenoxy acid herbicides doubled the risk of nasal and nasopharyngeal cancer (relative risk 2.1, not statistically significant). The controls used for this study were the same as those used in the previously mentioned Swedish studies of sarcomas and lymphomas.

Tung reported that primary liver cancer occurred in excess in Vietnam as a result of Agent Orange exposure of the general population, but this reported excess was not verified when his report and pathologic specimens were reviewed (VA lit rev., 1981). Even though human liver damage has been reported as a result of dioxin exposure (see above), no excess liver cancer has been reported.

1.6. Reproductive Effects

The reproductive effects of 2,4-D, 2,4,5-T, and TCDD, alone or in combination, have been examined in a number of different animal species. The effects are variable, depending on dosage, species, and strain. Only animal studies of the effects of 2,4,5-T with levels of TCDD contamination which either are unknown or known to be at least 1 ppm and of the effects of combinations of 2,4-D, 2,4,5-T, and TCDD will be discussed, in the light of the composition of Agent Orange.

A study of the effect of exposure of male mice to contaminated 2,4,5-T before mating with unexposed females showed no effect on the loss of fetuses before or after implantation (Buselmaier et al., 1972). Lamb et al. (1980) examined the effects of "simulated Agent Orange" -- i.e., mixtures of 2,4-D, 2,4,5-T, and TCDD -- administered to male mice followed by mating to untreated females. No effects were reported in fertility, implantation, fetal malformations, germ cell toxicity, sperm concentration, motility, or abnormalities and survival of offspring.

Most of the reproductive studies in animals have involved exposure only of the female after conception. In monkeys, fetal size was reduced but no malformations were observed (Wilson, 1971). In the rat, low doses of 2,4,5-T produced cystic kidney and intestinal hemorrhage (Courtney et al., 1970; Sparschu et al., 1971). A slightly increased incidence of cleft palate in the rat was reported in one study (VA, 1981 lit. rev.). 2,4,5-T administered throughout gestation produced maternal toxicity, fetal death or decreased fetal growth (Hall, 1972). In the mouse, 2,4,5-T produced cleft palate, and cystic kidney, the necessary dosage depending on the strain (Bionetics, 1968; Courtney et al., 1970; Gaines et al., 1974). In the hamster, cleft palate was rarely encountered; instead abnormal cranial development was observed (Collins et al., 1971).

Reproductive outcomes have been examined after many human exposures. However, the significance of most of these studies is questionable because of limitations in study design, population size, and inadequate handling of confounding factors. Pazderova-Vejlupkova et al. (1980) considered the frequency of abortion to be normal among wives of workers in the Czech factory. Following the explosion at Seveso, no increase in congenital malformations or developmental abnormalities was noted, but it was not possible to assess the frequency of spontaneous abortions due to an increase in elective abortions following the accident, and no baseline data were available for miscarriages (Reggiani, 1979; Homberger et al., in VA lit. rev.). In the U.S.A., a study of the incidence of spontaneous abortions among women whose husbands were occupationally exposed to 2,4-D as farmers, forest workers, or herbicide applicators revealed no overall association (SRI International, 1981). Human miscarriages near a spray project near Globe, Arizona, were found not to be related to herbicide use; a similar lack of association was found with human malformations in Swedish Lapland (Binns and Balls, 1971; Advisory Committee, 1971). In Arkansas, facial clefts were not associated with the agricultural use of 2,4,5-T (Nelson et al., 1979). A study of birth defects in children born to Long Island Railroad maintenance employees exposed to 2,4,5-T used for weed control revealed that all major birth defects combined and inguinal hernia were less frequent than expected. An excess observed for metatarsus adductus and tear duct obstruction probably resulted from variability in diagnosing these "minor" defects (Honchar, 1982). Reproductive outcomes of wives of Dow Chemical employees exposed to dioxins were surveyed. No statistically significant association between exposure and spontaneous abortions, stillbirths, infant deaths, and congenital malformations was observed (Townsend et al., 1982). The reported association between 2,4,5-T spraying and an increased incidence of miscarriage in the Alsea basin of Oregon (EPA, 1979) has been severely criticized (Wagner et al., 1979; Mantel, 1979).

A number of studies of reproductive outcomes were conducted in Australia and New Zealand. A study in Australia revealed no relationship between 2,4,5-T use and birth defects (Aldred et al., 1978). Another showed a correlation between the season of conception of babies with neural tube defects and the season of maximum 2,4,5-T spraying; a correlation was also found between neural tube defects in animals and 2,4,5-T (Field and Kerr, 1979). Two studies in New Zealand found no association between 2,4,5-T exposure and neural tube defects (McQueen et al., 1977; Hanify et al., 1981). One of these also found no association with cleft lip and palate or malformations of the heart or male genitalia, although it did reveal an association with talipes (malformations of the foot). A study in Western Australia that suggested an association between cleft lip and palate and herbicide exposure (Brogan et al., 1980) has been criticized on methodologic grounds (Bower and Stanley, 1980). A survey of ground agricultural sprayers showed no differences in the occurrence of malformations, stillbirths, miscarriages, or ectopic pregnancies (Smith et al., 1981).

The reports of human birth defects alleged to result from exposure to Agent Orange, which appeared in South Vietnamese newspapers in 1969, caused public and scientific furor (Advisory Committee, 1971; Young et al., 1978). In response, two independent surveys of South Vietnamese hospital records were conducted. An apparent increase in certain birth defects relative to others, which seemed to be associated with periods of herbicide spraying, was noted by

Meselson et al. (1971). Cutting et al. (1970) found no increased incidence of congenital abnormalities, stillbirths, and hydatidiform moles with heavy herbicide spraying. However, the conclusions of both of these studies were seriously limited by incomplete and unrepresentative sampling of births, unreliable birth records, and inadequate estimation of exposure (Advisory Committee, 1971). A subsequent study found an increased prevalence of isolated cleft palate and spina bifida compared with earlier years before widespread defoliant use, which might, however, be attributable to better case-finding and referral (Herbicide Assessment Commission, 1970; Nelson et al., 1979). Tung et al. (1971) and Rose and Rose (1972) reported on malformations and abortions among South Vietnamese refugees in North Vietnam. Lack of specific information about exposure and the lack of an unbiased selection procedure preclude any causal inferences. Studies conducted in South Vietnam in 1972 and 1973 by the National Academy of Sciences (1974) found no conclusive evidence of association between human birth defects and herbicide exposure, although study limitations were recognized.

A report has just been released on a large study (Donovan et al., 1983) designed to determine if Australian Vietnam veterans are at increased risk of fathering babies with birth defects. Vietnam veterans had no greater risks than veterans who served elsewhere or than men who were not veterans.

1.7. Other Effects

Gastrointestinal problems have been reported after a number of human exposures. A health survey of workers involved in 2,4-D production revealed that about half complained of dyspepsia, abdominal pains, and constipation (Bashirov, 1969). About 30% of the workers studied at the Newark plant complained of gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pains, or blood in stool) (Poland et al., 1971). Digestive disorders were reported among workers in the factories in Grenoble, France, and in Hamburg and Middle Rhein, West Germany (Dugois et al., 1958; Schulz, 1957; Bauer et al., 1961). Gastrointestinal symptoms, including abdominal pains and indigestion, were among the delayed symptoms which developed 2 to 3 years after TCDD exposure in two of the three government scientists in England (Oliver, 1975).

High levels of serum cholesterol and lipids were also commonly reported among exposed workers. Serum lipids tended to be high among workers following the explosion at the Nitro factory (Suskind, 1978). Ten percent of Newark workers had elevated serum cholesterol levels (Poland et al., 1971). Hyperlipemia and hypercholesterolemia were reported among workers in Grenoble (Dugois et al., 1958). Similar findings were described for the Czech workers, who also exhibited elevated levels of pre-beta lipoprotein and of total blood proteins (Jirasek et al., 1974; Pazderova-Vejlupkova et al., 1980, 1981). All three of the English scientists had hypercholesterolemia (Oliver, 1975). Walker and Martin (1979) reported high cholesterol and triglyceride levels and low high-density-lipoprotein levels in a small group of exposed workers.

2. Diseases Affecting U.S. Troops in Vietnam

This section is included to provide background on the health of U.S. servicemen while they were stationed in Vietnam. Fifty-six to seventy-four percent (mean 70.6%) of hospital admissions during the Vietnam war were for

medical disorders, as compared with battle casualties (15.6%) and non-battle injuries (13.8%), during the period 1965-69 (Ognibene and Barrett, 1982). Despite this fact, the average annual disease admission rate (351 per 1,000 per year) was one-third lower than for the China-Burma-India and Southwest Pacific theaters in WWII, and 40% less than for the war in Korea (Neel, 1973).

Malaria has been identified as the most significant medical problem, accounting for the greatest number of man-days lost from duty during the war. The emergence of a chloroquine-resistant form of malaria, P. falciparum malaria, led to the use of Dapsone^{R} (4,4'-diaminodiphenylsulfone), which is also used to treat leprosy (Neel, 1973).

Infectious hepatitis did not pose a major problem during the Vietnam war, as it did in previous wars. The incidence of hepatitis (6.9 cases per 1,000 per year) varied with the intensity of combat operations and with troop interaction with the civilian population (Neel, 1973). In Vietnam, serum hepatitis was of more concern, occurring most commonly among men who received multiple blood transfusions related to battle injury or among those using illicit drugs intravenously (Ognibene and Barrett, 1982).

Diarrheal disease rates were also lower compared with earlier wars. The prevalence rate ranged from 69 per 1,000 in 1965 to 35 per 1,000 in 1969. Diarrheal diseases may have been related to viruses, bacteria or parasitic agents, but the cause of most cases could not be identified. Troops at greatest risk were those who were unacclimatized and those under combat conditions. Incidence peaked in May or June, corresponding with the monsoon season (Neel, 1973).

Skin diseases were quite prevalent among troops in Vietnam. Those cases severe enough to require hospitalization or retention in quarters varied from 30 per 1,000 in 1965 to 20 per 1,000 in 1968. In 1970, however, skin problems increased again, to 30 per 1,000. The reason for the increase is unexplained. The three major skin problems identified were superficial fungal infection, bacterial infection, and immersion foot (Neel, 1973; Allen, 1977).

Plague and cholera, endemic in the Vietnam population, did not pose a significant problem for U.S. troops. Melioidosis, an infectious disease of humans and animals endemic in tropical areas, presented a problem to U.S. physicians unfamiliar with its diagnosis or treatment. Two hundred and thirty cases, diagnosed between 1965 and 1971, resulted in 14 deaths (Neel, 1973). The problem of fever of undetermined origin (FUO) presented some of the most challenging diagnostic dilemmas for military physicians in Vietnam. The diagnosis of FUO ranked second only to venereal disease. During the period 1966 through 1969, 58 cases per 1,000 were reported each year, including hospitalized and non-hospitalized patients (Ognibene and Barrett, 1982).

Venereal diseases have been prevalent during most military engagements. In Vietnam, it led other common medical problems in prevalence from 1965 to the conclusion of the war. Gonorrhea accounted for 90% of all venereal disease cases. The second most frequently occurring condition of venereal origin was chancroid (Ognibene and Barrett, 1982).

Neuropsychiatric diseases did not differ appreciably among troops serving in Vietnam and those serving elsewhere until 1968. During this year, the prevalence of psychosis, psychoneurosis, and of character and behavior

disorders increased among all army troops and particularly among those stationed in Vietnam and became the second leading disease problem by 1970. Concomitantly, the problem of drug abuse escalated during this period, especially among younger, lower ranking enlisted men (Neel, 1973).

3. Current Health of Vietnam Veterans

Very little is known about the health of Vietnam veterans relative to the health of other men of similar age. Some indication of veterans' and others' perceptions about the veterans' health can be found in the reports of Bogen, 1979; Stellman and Stellman, 1980; Texas Dept. of Health, 1983; UCLA-VA Protocol literature review; and Wolfe, 1980. The most frequently reported conditions include dermatologic disorders, neurologic and psychologic disorders (including numbness and tingling in the extremities, headaches, fatigue, depression, memory loss, sleep disturbances, and sexual dysfunction), reproductive problems (birth defects, miscarriages, abortions, reduced fertility), cancer, gastrointestinal disorders, infections, hypertension, hepatic hematologic, genitourinary, respiratory, and cardiovascular problems.

Although there is a lack of data on organic disease outcomes among Vietnam veterans, there are a number of reports on the occurrence of health-related outcomes -- outcomes which may be considered by some to be disease outcomes and by others as possible causes or effects of disease.

Several large surveys have been conducted which provide psychological and sociological data on Vietnam veterans, veterans who served in the Vietnam era but not in Vietnam, and contemporary non-veterans (Starr et al., 1973; Martindale and Poston, 1979; Hammond, 1980; Harris and Assoc., 1971; Egendorf et al., 1981). These surveys present objective data concerning several aspects of social adjustment, subjective reports of psychological adjustment, and attitudes held by and about Vietnam era veterans. Although these surveys employed a variety of methods and focused on different aspects of adjustment, it can be concluded from this literature that Vietnam veterans have encountered more problems in adjusting to civilian life than the other men (Figley, 1977; 1978).

The general areas of observed or suspected sociological differences among Vietnam veterans, other Vietnam era veterans and non-veterans include educational and occupational status, stress-related psychological difficulties, drug and alcohol use, medical problems, and arrests (Boscarino, 1981; Boscarino and Figley, 1981; Segal, 1977; Borus, 1975; Gover and McEaddy, 1974; Stinson, 1979; O'Brien et al., 1980; Mintz et al., 1979). These problems have been found to vary among subgroups of these populations defined by ethnicity, exposure to combat, urban or rural residence, and period of service in Vietnam (Egendorf et al., 1981; Penk et al., 1981).

Post Traumatic Stress Disorder (PTSD) and its association with Vietnam service, exposure to combat, and drug and alcohol use has been widely investigated (Roberts et al., 1982; Boman, 1982; Lipkin et al., 1982; Frye and Stockton, 1982; Wilson & Kruass, 1982; Boscarino, 1980; 1981; Helzer et al., 1979; DeFazio et al., 1975; Horowitz, 1975). PTSD is thought to be a very common condition among Vietnam veterans (Wilson, 1980). However, large-scale psychiatric epidemiology research, which treats PTSD as a distinct diagnosis, has not yet been reported. Reliable estimates of the prevalence of PTSD in

the Vietnam veteran population cannot be derived from the current literature because of the frequent use of unusual (e.g., treatment seeking) samples and because symptom frequencies instead of validated diagnostic criteria have been used as outcome measures.

4. Long-Term Health Status of Servicemen and Veterans

This literature was reviewed to provide background for the Vietnam Experience study. The writers of these protocols expected to find a rich literature, but did not.* Numerous health studies of veteran populations have been conducted, but there are few, if any, which deal with long-term health effects of the general war experience. Disease incidence and prevalence among army personnel is well documented for World War II (WWII) (Anderson, 1968), the Korean War (Army Medical Service Graduate School, 1954), and the Vietnam conflict (Ognibene and Barrett, 1982) (see part 2, this Appendix); however, these reports cover only the period of military action.

*For reports of studies on the long-term health effects of war experience, we reviewed the Cumulated Index Medicus for the years 1975 through March 1983. In addition, several computer-based literature searches were conducted against these on-line data bases: Medline, 1966-83; Cancerlit, 1963-83; American Statistics Index, 1974-82; Social Science Citation Index, 1972-83; Psych Info, 1967-83; and Sociological Abstracts, 1963-83. The holdings of the libraries maintained at the Centers for Disease Control, Veterans Administration (VA) Hospital (Atlanta), VA Central Office (Washington) and Emory University School of Medicine were reviewed for appropriate reports. Finally, relevant studies completed on veteran populations by the Medical Follow-up Agency of the National Research Council within the National Academy of Sciences were included in the literature search. When relevant studies were identified, we used a branching technique to search for other cited references. A total of 135 journal articles and books were brought to CDC offices and reviewed.

A summary of the studies reviewed follows, even though they are not especially useful for the task at hand.

Hawryzluk (1975) studied prevalence ratios of diagnosed conditions among 813 army officers. Hearing loss, musculoskeletal disorders, and skin disorders were among the most frequently occurring medical problems. This study was limited to officers, most of whom were between 33 and 37 years old and had had 10-14 years of military service. They were selected for leadership positions and for their potential ability to do college work; thus, they were probably not representative of the general military population.

Medical records from the Armed Forces and the VA offer opportunities for followup studies. The Armed Forces system records all illnesses and injuries, even minor ones, among its active duty members, and it stores the clinical records in a central repository when the individual is separated from service. In the VA system, records documenting most of the agency's contacts with a veteran are maintained in a single file. Because benefits to veterans are many and varied, the VA maintains contact with most veterans, and many thousands of records are thus accessible for study (DeBakey and Beebe, 1962), (Beebe, 1951), (Cohen, 1953). However, because only a fraction of veterans receive their health care at VA facilities, and because those who do may be less educated and have more severe service-connected physical and mental disabilities, the records are of questionable usefulness for epidemiologic purposes, since their health experiences may not reflect those of the overall veteran population.

Armed Forces and VA records have been used for clinical followup studies of various medical and traumatic conditions, such as leprosy (Brubaker et al., 1969), rheumatic fever (Engleman et al., 1954), missiles in the heart (Blano and Beebe, 1966), and psychoneuroses (Brill and Beebe, 1951). These studies have been conducted for the purpose of describing the natural history and progression of the disease or condition and were conducted without control groups. Other studies with control groups, on the basis of the Armed Forces and VA data bases, have been directed at the veteran population receiving health services through the VA system, for example: studies of amyotrophic lateral sclerosis (Kurtzke and Beebe, 1980), asthma (Robinette and Fraumeni, 1978), scrub typhus (Elsom et al., 1961), coronary heart disease (Hrubec and Zukel, 1974), lumbar disc lesions (Hrubec and Nashold, 1975), splenectomy (Robinette, 1977), infectious mononucleosis (Miller and Beebe, 1973), cirrhosis of the liver (Beebe and Simon, 1970), esophageal cancer (Rogers et al., 1982), traumatic limb amputations (Hrubec and Ryder, 1980), and learning and reaction time (Milligan and Powell, 1981). Generally, the controls for these studies have been other veterans. Since the diseased and control veterans in these studies were not stratified with respect to their combat participation, the effect of that experience on the occurrence of the disease or its clinical course cannot be evaluated.

Veterans or their families have been participants in several studies on the effect, on subsequent health, of exposure to certain risk factors. Wallis (1968) reported on stress in service families, but his study did not include control families. Other studies have examined the effect on veterans of exposure to adjuvant influenza virus vaccine (Beebe et al., 1972), microwave radiation (Cleary et al., 1965), mustard gas (Beebe, 1960), (Norman, 1975), and smoking (Rogot and Murray, 1980). These studies included control groups,

but they were also selected from among other veterans. For the reasons discussed above, these data cannot be used to evaluate the effect of war service.

The literature contains reports from several studies that examined the morbidity and mortality experience of prisoners of war (POW's). Nefzger (1970) found that standardized mortality ratios and death rates indicated a clear early excess of deaths among prisoners held by the Japanese in WWII. Prisoners from the European and Mediterranean theatres of WWII did not have an adverse mortality experience to 1965. Keehn (1980) followed the same groups through 1975 and found that their increased risks of death, though diminished over time, persisted for 9 and 13 years, respectively. Mortality in Korean War prisoners has been more like that in Pacific than European WWII prisoners (Nefzger, 1970). Mortality from tuberculosis and from trauma contributes to the increase among Pacific ex-prisoners, whereas for Korea the increase is limited to trauma. An excess of deaths due to cirrhosis of the liver was apparent in all three former prisoner groups, WWII (Europe, Pacific) and Korean, from about the 10th followup year (Keehn, 1980).

Beebe (1975) studied morbidity, disability, and maladjustments among WWII and Korean prisoners and compared them with veteran controls from the same wars who were not taken captive. In this study, sequelae of the POW experience were both somatic and psychiatric and were of greatest extent and severity among Pacific WWII POW's. Among European WWII POW's, only psychiatric sequelae were apparent. Somatic sequelae were most prevalent in the early years after liberation, but for Pacific WWII POW's they persist in the form of higher hospital admission rates for many specific causes. Klonoff et al. (1976) investigated the long-term or residual effects resulting from severe and extended exposure to stress among POW's captured in Japan (high-stress group) or Europe (low-stress group) during WWII. The low-stress group was divided into long-term and short-term internment periods. Neuropsychological, psychiatric, and physical/neurological outcomes were compared, and significant differences were found among these three groups. The high-stress group scored significantly lower in operational intelligence, exhibited more signs of psychiatric maladjustment, and had more physical illnesses, especially of the neurological and musculoskeletal systems. Residual effects increased in proportion to length of internment, though numbers in each category were small when stratified in this way. The authors concluded that terms such as "survival syndrome" (Chodoff, 1963) and "war neurosis" (Maskin, 1966) describe identifiable phenomena with long-term residual effects (Klonoff et al., 1976).

Davies (1978) found an excess of leukemias, lymphomas, myelomas, and polycythemia vera among Australian servicemen with overseas and tropical area service as compared with those serving in temperate Australia; however, he did not control for confounding variables (such as age) and, for some controls, the area of service was doubtful. A diagnosis of malaria and/or an interaction of nitrates and nitrites with the malaria prophylactic drug chloroquine were suggested as possible risk factors. In a followup study, Giles et al. (1980) investigated the possibility that exposure to malaria may have led to later development of lymphoma in 62 men resident in Tasmania, Australia, and found no association.

In two studies which covered 29 years (1946-1974), Jablon and Miller (1970, 1978) found no statistically significant differences between army x-ray technologists (n=6,560) and controls (n=6,826) who served as medical, laboratory, or pharmacy technologists for total deaths from cancer, individual site of cancer, or deaths from other causes. Norman et al. (1981) investigated exposure to tetrachloroethane by comparing age-specific mortality among 1,099 males assigned to chemical processing companies during WWII and 1,319 veterans not involved in the impregnation process of protecting clothing against mustard gas. Overall cancer mortality for exposed subjects was 1.26 times higher than for controls. The risks for leukemia, lymphoma, and cancers of the genital organs were moderately elevated, but the numbers were small and no significant excesses were observed.

The Medical Followup Agency of the National Academy of Sciences - National Research Council established a Twin Registry comprising 16,000 pairs of white male twins, both members of which had been in military service, mainly in WWII. This data base has provided information for the study of multiple sclerosis (Bobowick et al., 1978), cardiovascular and respiratory symptoms (Cederlof et al., 1969), (Hrubec et al., 1973), psychopathology (Pollin et al., 1969), (Allen and Pollin, 1970), (Hoffer and Pollin, 1970), (Stabenau et al., 1970), intraocular pressure (Schwartz et al., 1972, 1973), corticosteroid response (Schwartz et al., 1973), allergy (Bazaral et al., 1974), skin diseases (Lynfield, 1974), hypertension (Oglesby, 1975), headache (Ziegler et al., 1975), plasma cholesterol and triglycerides (Christian et al., 1976), personality traits (Horn et al., 1976), earnings (Taubman, 1976), dietary intake (Fabsitz et al., 1978), weight changes (Fabsitz et al., 1980), electrocardiographic characteristics (Havlik et al., 1980), alcoholism (Hrubec and Omen, 1980), and familial factors in early deaths (Hrubec and Neel, 1981). These studies have not classified the veterans according to their combat experience.

Seltzer and Jablon (1974) found evidence for a "healthy warrior" effect when they examined the effect of health selection at induction on subsequent cause-specific mortality in a series of 85,491 white male WWII U.S. Army veterans followed for 23 years, 1947-1969. They found that mortality rates were well below those of the general population during the first few years after discharge. After 23 years the mortality rates of the veterans were still lower than, but approaching, those of the general population. The effect of military selection varied considerably according to the nature of the cause of death.

Three studies have demonstrated an association between mortality and military rank at separation from military duty. Keehn et al. (1978, 1974) and Seltzer and Jablon (1977) found that mortality during 24 years following separation declined with each successive advance in rank through the enlisted grades. Furthermore, mortality of privates was very close to expectation based on population rates; non-commissioned officers had a 23% advantage and commissioned officers about a 40% advantage. The advantage held for deaths from all causes and also for most specific causes examined. Over the 24-year period of followup, the tendency for the differences to diminish was only small.

In summary, many health studies have been conducted on veteran populations, but because of the lack of control groups, the selection of control groups from among veterans who were not classified as to their combat experience, and the selection of study subjects from specific military occupational specialties, the studies are not useful for evaluating the overall effect of war service. CDC's review of this literature revealed little which could be used to generate specific hypotheses about health effects of military service in the Vietnam war.

APPENDIX C
SAMPLE SELECTION USING TELEPHONE RANDOM DIGIT DIALING

Random digit dialing is a telephone sampling method that produces a random sample of households with telephones, regardless of whether or not the number is listed in the telephone directory. It appears to be an efficient and inexpensive means of obtaining an unbiased random sample, and a preferable alternative to time-consuming and costly door-to-door screening and to random selection of numbers from telephone directories or specially compiled lists. The latter approach misses unpublished and new listings and requires the difficult task of removing duplicates when large geographic areas and multiple overlapping directories and lists are involved. Further, since 90.2% of all U.S. households had telephones in 1976 (thought to be around 95% in 1983), biases attributable to underrepresentation of those households that do not have telephones are not likely to affect results appreciably (Klecka and Tuchfarber, 1976). One factor to be aware of, however, is that availability of telephones is related to income. According to the 1970 Census of Population and Housing, 76% of households with incomes $5,000 had telephones, compared with 95% of households with incomes |$25,000; 89% of white households had telephones, compared with 70% for black households (Waksberg, 1978).

Random digit dialing methods range from dialing a 7- or 10-digit random number to compiling a listing of area codes plus 3-digit exchanges used within the geographic bounds from which a study sample is to be drawn and randomly appending the last 4 digits. The 7- and 10-digit random numbers are estimated to produce households for only 1 in 30 and 1 in 200 numbers dialed, respectively (Cooper, 1964; Glasser and Metzger, 1972). Sampling within the listing of area code plus 3-digit exchanges involves one of several approaches to randomly append the last 4 digits and to deal with non-residential and not-in-service numbers. Klecka and Tuchfarber (1974a) report that the proportion of not-in-service numbers ranged from 37.3% in an urban setting to 70.6% in a rural region for 3 random digit dialing samples; and the proportion of business numbers were 11.3% and 3.2%, respectively. Cooper (1964), who uses blocks of 3-digit exchanges plus 1 digit and randomly selects the remaining 3, reports 32% of the numbers were ineligible. Waksberg (1978) contends that simple random sampling within existing exchanges is inefficient, since about 80% are businesses, institutions, government, or not in service. Waksberg's method seems to eliminate making large numbers of nonproductive calls to non-residential and not-in-service numbers by making multiple calls within a block of numbers (block=area code + exchange + 2 random numbers) only if the first number dialed within that block is residential.

To support the hypothesis that random digit dialing yields an unbiased sample, such a sample must be scientifically compared with samples drawn by conventional means in the field. In 1974, Klecka and Tuchfarber (1976) compared their random digit dialing sample on crime victimization of 800 households and 1,685 respondents in Cincinnati, Ohio, with the Census Bureau's survey of 9,708 households and 19,903 respondents. Race, age, sex, education, income, household density of persons over 12 years of age, and ownership status of the residence were among the demographic variables examined. Excepting education, there were no statistically significant differences between the two populations when tested by chi-square. Thus, the authors concluded that random digit dialing and Census Bureau's complex approach had produced samples from the same population. References cited above and others documenting the efficacy of random digit dialing are found in section 12.

APPENDIX D

TOPICAL LIST OF QUESTIONNAIRE ITEMS* FOR AGENT ORANGE AND VIETNAM EXPERIENCE STUDIES

ADMINISTRATIVE

- Name
- Identification Numbers
  - Military Service Number
  - Social Security Number
- Telephone Number
- Interviewer Name
- Date of Interview
- Quality of Interview
- Names and addresses of friends who will know future whereabouts

SOCIODEMOGRAPHIC

- Date of Birth
- Place of Birth
- Current Residence
- Race/Ethnicity
- Marital History
- Education
- Religion
- Occupation and Income
- Problems in Obtaining Employment

MEDICAL

- Height and Weight
- General Health Status
- All Hospitalizations and Operations
- Physician Treatment, Physician Diagnosis, or Self-Diagnosis of:
  - Neurologic Disorders
  - Psychologic Disorders
  - Impaired Fertility
  - Endocrine Diseases
  - Cardiovascular Diseases
  - Cancer
  - Gastrointestinal Disorders
  - Genitourinary Disorders
  - Respiratory Diseases
  - Musculoskeletal Condition
  - Dermatologic Conditions
  - Other Complaints
- Trauma
- Reproductive History
- Blood Transfusions

*Some data items listed may be derived from military records.

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

Smoking
Alcohol
Abbreviated Occupational History Focusing on Exposures to Herbicides
Illicit Drug Use

MILITARY HISTORY

Drafted/Enlisted
Countries of Assignment
Occupational Duties
Combat Intensity
Injuries, Wounds in Service
Herbicide Exposure

APPENDIX E
TOPICAL LIST FOR EXAMINATION AND LABORATORY TESTING*
AGENT ORANGE AND VIETNAM EXPERIENCE STUDIES

PHYSICAL EXAMINATION

The physical examination will be modified from those of the National Center for Health Statistics' Health and Nutrition Examination Survey and the Ranch Hand Study, with special attention given to the dermatologic and neurologic systems.

General: habitus, weight, height, blood pressure, pulse, respiratory rate
Skin: rash, scars, ulcers, acne, masses, spider angiomata, pigmentation
Head: movements, hair pattern
Eyes: movements, fundi, Snellen testing of acuity, conjunctiva, icterus
Ears: audiometry, otoscopic exam
Nose: polyps, sinusitis
Mouth: teeth, tonsils, tongue, cheeks, throat, gingiva
Neck: thyroid and parotid palpation, cervical lymphadenopathy
Chest: movements, bony abnormalities, axillary lymphadenopathy
Lungs: rales, rhonchi, wheezes, dullness, hyperresonance
Heart: extra sounds, murmurs, rubs, size
Abdomen: liver and spleen size, tenderness, masses, hernias, testicular size and masses, inguinal lymphadenopathy, rectal exam
Back: scoliosis, kyphosis, tenderness
Limbs: movements, edema, arthritis, varicosities, nail clubbing, peripheral pulses, lymph nodes
Neurologic: mental status, cranial nerves, motor system, reflexes, sensory deficits, nerve conduction studies (conduction evaluation only for Agent Orange study)

PSYCHOLOGIC AND NEUROPSYCHOLOGIC TESTING

Minnesota Multiphasic Personality Inventory
Diagnostic Inventory Schedule
Psychiatric Epidemiology Research Interview
Battery from Halstead-Reitan Neuropsychological Tests
Armed Forces Qualification Test--this is the intelligence test given to the veterans on their induction into service
Wechsler Memory Scale

* May be modified as a result of consultations to take place in late 1983 and early 1984 with experts in several specialties, e.g., neurology, immunology, psychology.

LABORATORY TESTING

BLOOD:

- Complete Blood Count: hematocrit, red cell count, white cell count and differential, platelet count
- Fasting Blood Glucose
- Cholesterol and Triglycerides
- Creatinine
- Bilirubin and GGPT
- Thyroxine
- Hepatitis B Core Antibody
- Serum Stored for Future Serologic Testing

URINE:

- Protein
- Glucose
- Hemoglobin
- Porphyrins

STOOL:

- Qualitative Test for Occult Blood

MISCELLANEOUS:

- Delayed Cutaneous Hypersensitivity Battery:
  - Mumps
  - Candida
  - Tuberculin
  - Streptococcus
  - Proteus
  - Diphtheria
  - Tetanus
  - Control

APPENDIX F

TOPICAL LIST OF QUESTIONNAIRE ITEMS FOR SELECTED CANCERS CASE-CONTROL STUDY

ADMINISTRATIVE

- Name
- Identification Numbers
  - Military Service Number
  - Social Security Number
- Telephone Number
- Interviewer Name
- Date of Interview
- Quality of Interview
- Friends who will know future whereabouts

SOCIODEMOGRAPHIC

- Date of Birth
- Place of Birth
- Current Residence
- Race/Ethnicity
- Marital Status
- Education
- Religion
- Occupation and Income

FAMILY HISTORY OF CANCER

Occurrence of soft tissue sarcomas, lymphomas, and other cancers in first-degree (parents, siblings, and children) and second-degree (aunts, uncles, and grandparents) blood relatives and spouses.

MEDICAL

- Height and Weight
- Possibly Predisposing Conditions
  - Immune Deficiency Diseases
  - Rheumatoid Arthritis
  - Other Cancers
  - Celiac Disease/Gluten Enteropathy
  - Hemophilia
  - Infectious Mononucleosis
  - Neurofibromatosis
  - Trauma
- Medical Exposures
  - Immunosuppresive Therapy
  - X-irradiation
  - Dilantin
  - Iron Dextran
  - Blood Transfusions
- Surgery, Hospitalizations, Long-term Medications
- Medical Care Utilization

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

- Smoking
- Alcohol
- Lifetime Occupational History, Including Probes to Exposures Such As:
  - Asbestos
  - Herbicides
  - Pesticides
  - Irradiation
  - Organic Solvents
  - Vinyl Chloride
  - Benzene
  - Arsenicals
  - Wood dust
- Illicit Drug Use

MILITARY HISTORY

- Drafted/Enlisted
- Training
- Countries of Assignment
- Military Occupational Specialty
- Occupational Duties
- Combat Intensity
- Herbicide Exposure

Use of trade names is for identification only and does not imply endorsement of the Public Health Service or the Department of Health and Human Services.

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