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DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

January 11, 1984

MEMORANDUM TO: Members, Science Panel
Cabinet Council Agent Orange Working Group (AOWG)

FROM : Dr. Peter E.M. Beach
Executive Secretary, Staff Director AOWG

SUBJECT : Review materials for January 26, 1984 Science Panel Meeting

At the request of Dr. Carl Keller, Chair Pro Tem, Science Panel, the enclosed two documents are for your review prior to the meeting of the Science Panel on January 26, 1984 in Room 729, Hubert Humphrey Building, 200 Independence Avenue, S.W., Washington, D.C., 9:30 - 11:30 a.m.

Enclosures (2)
1. Protocol for Epidemiologic Studies
2. Response to Scientific Reviews

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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

November 1983

U.S. Department of Health and Human Services
Public Health Service
Centers for Disease Control

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 emanated from Vietnam.

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

2.3. Diseases Affecting U.S. Troops in Vietnam

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

2.4. Current Health of Vietnam Veterans

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

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

2.5. Long-Term Health Status of Servicemen and Veterans

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

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

3. Study Design Overview

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

3.1. Agent Orange Study

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

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

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

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

		Likely Herbicide Exposure	
		Yes	No
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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November 1983

RESPONSES TO SCIENTIFIC REVEIWS OF THE CENTERS FOR DISEASE CONTROL'S DRAFT PROTOCOLS FOR EPIDEMIOLOGIC STUDIES OF THE HEALTH OF VIETNAM VETERANS.

RESPONSES TO SCIENTIFIC REVIEWS OF THE CENTERS FOR DISEASE CONTROL's DRAFT PROTOCOLS FOR EPIDEMIOLOGIC STUDIES OF THE HEALTH OF VIETNAM VETERANS

The Centers for Disease Control (CDC) released its draft document "Protocols for Epidemiologic Studies of the Health of Vietnam Veterans" on June 30, 1983. The document was reviewed by 4 separate scientific panels:

A) Office of Technology Assessment ("OTA Review")

Panel meeting held in Washington DC on June 24, 1983, and attended by representatives of CDC study team. Written review received by CDC on July 7, 1983.

B) Advisory Committee on Special Studies Relating to the Possible Long Term Health Effects of Phenoxy Herbicides and Contaminants ("Ranch Hand Panel Review")

Panel meeting held in Washington DC on July 19, 1983, and attended by CDC study team representatives. Written review received September 8, 1983.

C) Agent Orange Working Group Science Panel ("AOWG Review")

Panel meeting held in Washington DC on August 3, 1983, and attended by CDC study team representatives. Written review received on August 16, 1983.

D) Centers for Disease Control Ad Hoc Review Panel ("CDC Review")

This panel was composed of epidemiologists and statisticians drawn from CDC operating components not connected with the operating component responsible for the design and conduct of the study. Panel meetings were not attended by representatives of the study team. Written review received by the study team on July 8, 1983.

Comments were also solicited from several veterans' service organizations, and CDC study team representatives met with veterans representatives in Washington DC on August 31, 1983. At this meeting CDC described the scientific reviews and solicited further comments.

This document summarizes CDC's responses to the suggestions and criticisms contained in the written scientific reviews; responses to comments received from veterans' service organizations are interwoven in the reactions to the scientific reviews. The written reviews received from the 4 groups noted above are appended.

A) Responses to Office of Technology Assessment Review Suggestions

1) page 7 - Problem with proposed method for selecting Cohorts 1 and 2 for the Agent Orange Study

CDC concurs that "there is a possibility that one day a week sampling will misclassify some companies." The Army Agent Orange Task Force (AAOTF) has done further tests to determine the time required to abstract the company location information. This test involved construction of a partial history (all days, for a portion of 1967-1968) for the 1st Battalion of the 503rd Regiment, 173rd Airborne Brigade. It appears that it will be possible to abstract location information for 50 battalions for each of the days during the years 1967 and 1968. It is now estimated that this task will require 18 months. Even though this exceeds the 12 months allowed for this stage in the draft protocol timetable, CDC feels that the extra time required is well worth the delay -- concern about the sampling proposed in the draft protocol was one of the few issues consistently raised by all review panels. In order to minimize delay, CDC proposes to divide the ranking and sampling of units from the 50 battalions into 2 parts. During the first phase roughly 40% of the sample of individuals for the 2 cohorts will be selected. The sampling in the first phase will involve a ranking of 25 units and 40% of the ultimate sample of individuals will be derived from these units. In the second phase, all remaining units (i.e., the second 25 plus those not already chosen from the first 25) will be ranked and the remaining 60% of the sample will be derived from this ranking. The battalion tracking done by the AAOTF during the first phase will be completed in 12 months and this will allow CDC to begin interviews without delay.

2) page 9 - How will Cohort 3 for the Agent Orange study be selected?

The third cohort will be chosen from a list of all units operating in Vietnam in 1967-1968 which served only in areas where herbicides were not used. Examples of such places suggested by the AAOTF to CDC include Cam Rahn Bay, which was a large base located on a sandy coast where there would be no reason for herbicide use. Places suggested by the AAOTF as being candidate locations will be checked against the herbicide usage records for evidence of herbicide use; chosen units will be checked to ensure that they were not temporarily assigned to herbicide use areas.

Since combat units were frequently moved from place to place in Vietnam, it may be impossible to find combat units which (with certainty) did not serve in areas where herbicides were used. Learning about the location of units is a very time consuming process. Even if the massive effort to review the records of all combat units assigned to Vietnam was undertaken it could well prove wasted because combat units which only operated in herbicide-free areas may not exist. This concern is what brought CDC to recommend choosing the third

cohort from among units which had missions which would keep them in relatively circumscribed areas where there would be a fair degree of confidence about lack of herbicide usage. This approach may preclude including any combat units in the third cohort. However, in sampling from the list of units which will be constructed by the AAOTF, CDC will give preference to combat units if at all possible.

3) page 11 - Is the "luck-of-the-draw" assumption for the Vietnam Experience study valid?

CDC has been informed by the AAOTF that the regulations for staffing various commands during the Vietnam war precluded any selectivity, at least for certain Military Occupational Specialties. Thus the application of these procedures should have resulted in an essentially random assignment (conditional on occupational speciality) to Vietnam or other duty stations. What seems to be at issue here for some reviewers is the concern that the the regulations were not followed strictly or that somehow selectivity did indeed enter into the process. While there is probably no completely convincing test which can be applied at this time to evaluate the "luck-of-the-draw" assumption, CDC will make every effort to look for differences between those men who served in Vietnam and those who served elsewhere with respect to demographic and health characteristics which existed prior to service. These evaluations will be done first in the pretest and pilot study phase and will continue during the main study.

4) page 12 - Omit comparisons among those serving in different foreign environments

CDC concurs that the proposed comparisons of the effects of different service stations among the non-Vietnam cohort diffuses the focus of the study. In response to this criticism, CDC has altered the selection criteria for this cohort such that no attempt will be made to obtain a sample composed of equal numbers from Korea, Germany and the United States. Instead, the selection process will be designed so that those service areas will be represented in proportion to their military strengths during 1966-1971.

5) page 16 - Veterans' service organizations should aid in locating potential study participants

CDC has requested that some 15 veterans groups consider helping to evaluate the usefulness of searching for potential study participants through their organization membership rosters and other veterans lists in their possession. Those organizations which are willing to help will be provided with the names of 840 men for whom CDC has already begun tracing tests. If this approach proves useful, CDC will consider adding it to the other tracing procedures at its disposal.

However, it should be noted that there is some concern that the use of such tracing procedures might be unwise. This derives from an undocumented suspicion that members of the service organizations may somehow differ from non-members in such a manner that including a disproportionate number of them in the study (which could happen if such tracing procedures were quite successful) would distort the results.

6) page 17 - Mortality analysis

CDC concurs with the OTA suggestion that separate mortality analyses be carried out for 1) death certificate information alone, and 2) death certificate information supplemented with other data.

7) page 18 - Collect extensive birth defects data

CDC will collect information on reproductive histories from study participants during the interviews and examinations. Queries will be made about structural and functional deficits in their children. However, there are some reproductive questions which CDC believes are better answered by women than men. CDC has found in other studies that men do not have particularly good memories for certain adverse outcomes of their wives' pregnancies. CDC proposes that information gathered focus on questions where men can generally provide valid answers. To do more would require questioning spouses, and this would result in a substantial increase in resource outlay and could cause delay in completing the study. CDC does not feel that this is warranted since the major concerns (structural or functional deficits in offspring) can be adequately addressed by questioning men.

8) page 19 - Perform chromosome studies

Since sentiment for doing chromosomal analyses has been expressed by OTA and some other reviewers, CDC has re-examined the possibility of including them in its test battery. After this deliberation, CDC remains convinced that it would be unwise to include them. Most importantly, the sensitivity and specificity of these tests for current or future disease is unknown. Moreover, chromosome aberrations most strongly reflect current exposures to clastogens (e.g., smoking). CDC's experience with the Love Canal chromosome study suggests that securing appropriate laboratory capability will be difficult. Two of the best labs in the nation did the cytogenetic analysis for this study. It took them 10 months to process specimens from about 100 individuals and there were substantial intra- and inter-laboratory variations in results. If it is decided by the various review panels that such testing is mandatory, CDC would probably follow the OTA suggestion to do tests on 500 men per cohort, if it is possible to secure the necessary laboratory capability. This addition to CDC's procedures would require extra funds (probably on the order of $2.0 million) since these tests were not included in CDC's budget projections.

9) page 19 - Do sophisticated liver function tests

CDC is currently consulting with several clinical and laboratory experts on liver disease regarding the most appropriate non-invasive tests of liver function.

10) page 20 - Psychological and neurological testing consultants

CDC recognizes the importance of using epidemiologic methods and instruments which will be comparable to other major veteran and national mental health surveys. CDC is consulting with representatives of the National Institute of Mental Health (NIMH) Division of Biometry and Epidemiology and with The VA Office of Readjustment Counseling. CDC is also consulting with non-government experts who have contributed to the NIMH Epidemiologic Catchment Area studies and other important developments in psychiatric epidemiology.

11) page 21 - CDC may be forced to release data prematurely

The CDC study team will work with the CDC's General Counsel's office to explore ways to prevent premature release of data.

12) page 22 - Agent Orange or Vietnam experience "syndromes"

As noted by OTA, it will be important to try to determine if a syndrome of signs and symptoms might be associated with Agent Orange exposure or Vietnam service. In the words of the OTA reviewers, "This is an undoubtedly difficult and perplexing aspect of the study, but also the most critical." If such a syndrome exists, its detection will require that data on at least some of the signs and symptoms comprising the syndrome will have been collected (impossible to ensure a priori) and that the statistical analysis is adequate to detect the syndrome in the data at hand. CDC statisticians will be working to design the appropriate analyses over the course of the study.

13) page 24 - Questions about the power of the Sarcoma/Lymphoma study

The rationale for CDC's power calculations for detecting 2-fold increases in the risk for Vietnam veterans in the Sarcoma/Lymphoma study was not fully presented in the draft protocol. This oversight and other factors prompted OTA to comment that CDC may have overestimated the power of the study by overestimating the prevalence of Vietnam service among men in the target age range in the geographical areas covered by the SEER centers. Further, OTA has suggested that it might be more appropriate to design the study to be only powerful enough to detect a higher relative risk, say 5 to 7 instead of 2, since the Swedish studies which have detected increased risks among men occupationally exposed to 2,4,5-T found risks of that magnitude.

Because of the above mentioned Swedish studies of occupational exposure to 2,4,5-T, a specific concern has been raised about Vietnam veterans' risk for lymphoma and sarcoma. Thus an appropriate approach to the design of this study would be to ensure that it was capable of detecting, say, a 5 to 7-fold increase in risk among those with "meaningful" exposure. As was noted in the draft protocol, it is difficult, in the Vietnam context, to define "meaningful" exposure. Thus CDC chose to design the study to be fairly sensitive to a substantially lower increase in risk among all Vietnam veterans. The plan to use an exposure classification system similar to that developed for CDC's birth defects study will strengthen the study by providing an exposure scale. However, this exposure scale will only allow CDC to segregate Vietnam veterans on a qualitative and subjective basis (e.g., low, medium, high) and will not provide us with an unequivocal basis for separating those with "meaningful" exposure.

The concern of OTA that the prevalence of Vietnam service in the SEER areas may be around 8%, which is slightly outside the 10-15% range originally proposed by CDC, can now be seen from a different perspective: the uncertainty about the prevalence of Vietnam service pales in comparison to the uncertainty which motivates CDC's basing the power calculations on a 2-fold increase in risk. Even if one does not consider the issue from this perspective, the power difference between 8% and 10% is relatively insignificant. Therefore CDC does not concur with the suggestion that surveys be done in the ultimately cooperating SEER areas to determine prevalence of Vietnam service. In order that this study can encompass the majority of men who could have been conceivably exposed to herbicides in Vietnam, the revised protocol calls for the addition of men with birth dates 1929-1932 (see CDC review response #11 for a related suggestion). The addition of men with these birth dates results in an estimated Vietnam veteran prevalence of 7.5% in the SEER areas, using the method of computation used by OTA in its review of CDC's draft protocol. The revised protocol includes power estimates for prevalences of 5, 7.5 and 10% for a 2-fold increase in risk among Vietnam veterans in general. In addition, power calculations have been added for several possible levels of actual exposure to Agent Orange among all Vietnam veterans.

An individual reviewer for the Agent Orange Working Group Science Panel pointed out that in the Swedish data only about 50% of soft tissue sarcomas were coded to the ICD category 171 and suggested that CDC should review other codes for other sarcomas (see AOWG review response #30). In consultation with National Cancer Institute staff and other researchers, CDC has constructed a list of histologically-based codes to obtain a larger number of cases. CDC has revised its estimate of the number of cases available for study based on this expanded list. This new estimate is more than double the estimate presented in the draft protocol and has a marked effect on the projected power of the study. It is possible that this approach will result in some wasted effort. The final classification of tumors will be done by the special pathology review panel, in most instances after the cases have been interviewed. It is anticipated that the expanded list will include a larger proportion of cases which will be removed from the study because they are judged inappropriate by pathology panel than would be expected if the study were limited to cases coded to the ICD category 171. The revised estimates of

numbers of cases and power have been included in the final protocol and the power estimates noted in the paragraph above take account of these larger numbers.

14) page 26 - Add diseased control group to Sarcoma/Lymphoma study

The usual motivation for including a diseased control group in a study like the sarcoma/lymphoma study is fear that cases will have a different level of recall than will non-diseased controls. The most serious recall bias would involve the primary outcome variable. For the sarcoma/lymphoma study the primary outcome variable is military service in Vietnam and exposure to herbicides. CDC feels that there should be little worry about differential recall of Vietnam service. Furthermore, estimates of herbicide exposure will be derived from military records. Thus the addition of a diseased control group to this study would have to be motivated by fear of differential recall of potentially confounding factors. If reviewers feel that the addition of a diseased control group is essential for the study, CDC seeks advice as to what specific diseases should be eligible. Under the case ascertainment system to be used, a diseased control group would almost certainly need to be drawn from among men who have contracted other forms of cancer. Since most of the SEER programs only have permission from their cooperating hospitals to ascertain cancer cases, only cancer patients could be chosen as controls. CDC would suggest choosing patients with a variety of the rarer types of cancer. This would seem preferable to making use of cases affected by 1 or 2 of the more common cancers because of the possibility that those chosen might turn out to be related to herbicide exposure. This multiple cancer-type approach would fail if herbicides were the cause of a wide variety of cancers, although this possibility seems unlikely. Because the sample size calculations done for the 2 cohort studies were based in part on the expected frequency of all cancers, CDC notes a degree of the illogical in the proposal to use multiple cancer types. One of the individual reviewers for the Agent Orange Working Group Science Panel has suggested the use of colon cancer cases as a control group. This suggestion was made since colon cancer "...was specifically tested by the Swedes and found not to be associated with exposure to phenoxy herbicides." (The "Swedes" are the investigators who have done the studies which raise the suspicions about a dioxin-sarcoma/lymphoma connection.)

15) page 27 - Classification of cancers for Sarcoma/Lymphoma study

The final classification of cancers for this study will be done by special pathology panels after review of histological material provided by the SEER centers. The choice of cases for review by these panels will depend on a review of SEER center data for all diagnostic categories which might include cancers of interest. The SEER centers code in situ cancers and true malignancies by both topography and morphology. The topographical classification includes the ICD code "171", which pertains for tumors of connective, subcutaneous and other soft tissues. Exclusive use of this classification would result in omission of soft tissue sarcomas coded to other organs or sites. See also response #13 above.

Responses to Individual OTA Reviewer Suggestions (only those suggestions not addressed above)

Reviewer 1

16) page 4 - Blinding interviewers and examiners

For the Agent Orange study component, neither the study participants nor the interviewers and examiners will be aware of the cohort assignment of individuals. Examiners and participants will be asked not to discuss the participants' opinions regarding personal exposure. Blinding of study participants as to their own cohort membership for the Vietnam Experience component will not be possible -- they will know that they did or did not serve in Vietnam, but they will be requested not to discuss place of military service with their examiners.

17) page 4 - Credentials of CDC study team members

Credentials will be made available to OTA on request.

Reviewer 2

18) page 6 - Exposure information derived during the interview

CDC will question participants in the Agent Orange study about their perceptions of herbicide exposure and it may be possible to make comparisons making use of this type of information. It also may be possible to compare the health of men who developed acne while in Vietnam with those who did not. However, it will not be possible to segregate the participants with any degree of confidence into groups based on the presence or absence of symptoms of acute exposure to dioxin, because of problems of diagnosis and reporting.

Reviewer 3

19) page 7 - Selection of participants for the examination phase

CDC does not agree with the suggestion that participants invited to undergo physical examination should be selected on the basis of answers to questions which might suggest illness related to Agent Orange exposure. This issue was discussed at the OTA review meeting and CDC agrees with the summary OTA report statement (page 21) that "Although there remains some sentiment among some OTA advisory panel members that enrichment is advisable, the more general consensus is that not enough is known to do it."

It has also been suggested that "enriching" the examination sample on the basis of interview responses might be helpful in order to validate responses to interview questions. For example, participants who state in the interview

that they have high blood pressure could be preferentially selected so that their pressure could be measured by the study examination team. The major difficulty with this approach is that there are so many potential health measures for which this sort of validation might be desirable that the whole examination sample would comprise those who claim to have problems during the interview. It should be noted that evaluation of interview response validity will be possible under CDC's proposal of choosing a random sample of 2000 men for the examination, although not with the same precision as would be possible if the sample were "enriched."

20) page 7 - Use of consultants to help develop examination and laboratory protocols

CDC is seeking the advice of expert consultants for several major aspects of these protocols, including immunological, neurological, psychological, and statistical.

21) page 7 - Expand the Sarcoma/Lymphoma study to include cases diagnosed in earlier years

There are a number of on-going studies of soft-tissue sarcoma which may help to increase our knowledge about the relationship between these tumors and herbicide exposure. However, so far as CDC is aware only 2 have been designed to specifically look at the issue in respect of the Vietnam war, while the remainder focus on manufacturing and other occupational exposures. Both studies focusing on Vietnam veterans differ substantially from that proposed by CDC. In consequence CDC cannot agree that information derived from its proposed study will be "superfluous." The New York state health department study, which has been completed recently but not yet published, dealt with soft tissue sarcoma (not lymphoma) cases which were diagnosed between 1962 and 1980 The proposed Veterans Administration-Armed Forces Institute of Pathology study will be limited to cases of soft tissue sarcoma diagnosed before 1975-1980, according to a draft protocol (March 1983). Thus neither of these studies address the issue of the possible herbicide-lymphoma association and both will provide information about sarcomas for shorter latent periods only.

The suggestion that CDC should include sarcoma and lymphoma cases diagnosed before 1984 has merit, but the fact that there are two studies which address sarcomas arising in a shorter latent period makes that need questionable. The relatively large number of cases of lymphoma available makes the expansion to cases diagnosed prior to 1984 unnecessary for the purpose of increasing the sample size.

Reviewer 4

22) page 9 - Number of examination centers

CDC appreciates the possibility that having several examining centers might make it more convenient for participants and that added convenience will probably increase participation. However, as noted in the draft protocol, a minimum number of centers will enhance the possibilities for gathering high quality data. Until CDC has received proposals from parties interested in performing the examinations, it will be impossible to specify how these two competing interests will be balanced.

23) page 9 - Protection of participants employment rights under Chapter 43 of Title 38

The possibility of a legal basis for ensuring that participants do not suffer employment discrimination as a result of the need to take time off from jobs for the examination phase has been explored with CDCs' General Counsel. The issue was also discussed at length at an August 31, 1983 meeting of CDC staff, the representatives of several veterans service organizations, and officials from the Department of Labor. The consensus is that the law does not apply to this situation.

Reviewer 5

24) page 9 - Limitation of study to draftees and short-term enlistees of the Army

This issue was discussed at the August 31, 1983 meeting of veterans representatives and CDC staff. No strong reservations were expressed about CDC's proposed limitation to veterans of the Army. However, the representative of one group voiced concern about limitation to draftees and short-term enlistees for the Agent Orange study (design considerations preclude the possibility of including commissioned and non-commissioned officers in the Vietnam Experience study). CDC has reflected on the issue and has decided that it is best to retain the limitation. The inclusion of other categories of veterans would add substantial labor to the process of selecting individual veterans for the study. CDC understands that many long-term soldiers had multiple tours of duty in Vietnam. Assignment of such veterans to specific cohorts would require review of the locations of all the units to which such individuals were assigned in all their tours to assess probable herbicide exposure. Another important factor is the desire for comparing groups which are as homogeneous as possible. Moreover, it seems reasonable to expect that if there are health effects of Agent Orange exposure which apply to short-term enlisted men these effects would also apply to longer-term men who experienced similar exposures. There are of course possibilities that health effects could be different in longer-term men, perhaps among those who had multiple tours of duty in Vietnam, but to research the possibilities adequately would probably require a separate study.

Reviewer 5

25) page 10 - Appointment of a veterans' representative to CDCs' advisory panel

CDC requested that an advisory panel or steering committee be formed to provide guidance on a regular basis. CDC was informed that the charter of the panel which has served as a steering committee for the Air Force's Ranch Hand study includes responsibility for monitoring other such federal research activities as are specified by the Agent Orange Working Group. This panel has reviewed CDC's draft protocol (see below) and may ultimately be given the responsibility for long-term oversight. In any event, the composition of the panel will not be determined or influenced by CDC since this would conflict with the spirit of independent monitoring. Concerned veterans should direct their comments to the Agent Orange Working Group. However, CDC makes the observation that Congress has dictated that the Office of Technology Assessment provide continuing study oversight and the OTA advisory panel includes veterans' representatives. In addition, CDC will continue to meet regularly with representatives of veterans service organizations.

Reviewer 6

26) page 11 - Degree of herbicide exposure from non-Ranch Hand applications

The statement in the draft protocol that non-Ranch Hand herbicide applications might have been a significant source of exposures is at this time largely conjectural. However, military officials with whom CDC has consulted feel that this may well be the case. An example would be the spraying of base-camp perimeters where there is little question of troop proximity.

27) page 12 - Numbers of workers exposed in industrial accidents

While a number of books and summaries present tables of occupationally exposed workers, these table typically give numbers of "affected" individuals (eg., VA literature review, Vol I, pp 5-11, 18), or "cases" (eg., Young, et al 1978 VI-13,14,17,18). As mentioned in the VA literature review (pp 5-21), most reports do not give the total number of exposed workers.

28) page 12 - Several specific comments about literature on herbicides and dioxins

Modifications have been made in the protocol.

29) page 12 - How can other cancers be added to the sarcoma/lymphoma study?

The cancer registries which will participate in this study ascertain cases of all forms of cancer except those skin cancers which are treated in physicians' offices. Thus it will be simple to include any type of cancer in the study.

30) page 13 - Ask participants about their perceptions of herbicide exposures

Questions on this matter will be asked of all participants.

Reviewer 7

31) page 14 - Coordination with Veterans Administration Twin Study

CDC staff have paid a visit to the VA's Twin Study team in St. Louis and will continue to consult with its members.

32) page 14 - Elucidation of problems in interpretation of data because of Agent Orange study 3 cohort design

To determine the possible health effects of herbicide exposure, CDC needs to eliminate the possible influence of other factors inherent in the Vietnam service experience peculiar to those ground troops thought to have been most at risk of herbicide exposure. Comparison of cohorts 1 and 2 will remove the effect of the unique service experience, since both groups will be chosen from among units which had similar experiences. But if the herbicide usage or troop movement records are incomplete or inaccurate, then these two groups will suffer from misclassification of herbicide exposure because both will have operated in the general areas of herbicide use. If such misclassification is random, any difference in the health of the two cohorts due to exposure will be minimized. Comparison of cohorts 2 and 3 will give a measure of the effect of the unique experience free of the effects of herbicide only if cohort 2 is truly free of herbicide exposure. Comparison of cohorts 1 and 3 completely confounds the experience and herbicide exposure and can only be used to evaluate the combined effects of both factors relative to the absence of both. If a fourth cohort were available, one which had been exposed to herbicides but not to the experience, the analysis could be more comprehensive, even including a search for interaction between the experience and exposure.

33) page 14 - Is it possible for men to participate in the Agent Orange and Vietnam experience study?

The sampling schemes would make it possible for the same veteran to be chosen for both studies, but the selection probabilities for individual veterans for each of the studies is quite low so that this possibility should not present a practical problem.

34) page 14 - Record reasons for exclusion of units and individuals

The AAOTF will record reasons for exclusions of units and individuals.

35) page 14 - Reference for capture-recapture methods to estimate underascertainment of deaths

These methods have been used occasionally in epidemiological studies to estimate the size of a group when multiple incomplete data sources are used to ascertain the group members. See Hook, EB & Regal, RR, Am. J. Epid 116:168, 1982 for an application in estimating true number of babies born with birth defects.

36) page 15 - Differences in stated causes of death on hospital records and death certificates

CDC proposes using the cause of death recorded on death certificates for the primary mortality analyses for 2 reasons: 1)although imperfect, death certificate diagnoses will be available for virtually all the deceased, while more detailed information will likely be available for only a fraction, and 2) it will allow comparison with national cause-of-death data. Revised cause-of-death data from hospital records, autopsies, etc, will also be analyzed but special care must be taken in these analyses to assess possible differences in the quality of data from the different study groups (e.g., different autopsy rates).

37) page 15 - Power of study to detect increased cancer risks for specific types of cancers

The more plausible hypothesis is that herbicides/dioxin might increase the risk for one or a few types of cancer but not all cancers. The much lower power of the studies to detect increases in various specific types of cancer has been noted in the revised protocol.

38) page 15 - Problems with multiple analyses of the data

CDC shares the reviewer's concern about the potential problems of analyzing the data several times. Our motivation is, as was stated in the draft protocol, to be open to the possibility that we may discover an aspect that deserves more intensive study. It would be desirable to try to investigate the issue within the framework of these very expensive and time-consuming studies rather than be forced to begin a separate study of that issue. As a concrete example, consider the issue of infertility. At this point in time CDC feels that the question of infertility should be addressed by queries about reproductive performance. If it is found in the early analysis that there appears to be a difference between the groups in respect of fertility, then CDC would consider adding relevant laboratory procedures (e.g., sperm analyses, hormone assays) to the examination protocol.

39) page 15 - Choice of odds ratio as measure of effect for data analysis

Like much of the protocol, CDC's approach to issues of data analysis are presented in abbreviated form. More detailed plans will be developed as the studies progress and CDC will make use of the advice of non-CDC statistical consultants. By way of explanation of the protocol's focus on odds ratio estimates in the brief discussion of control of confounding, it may be noted that odds ratios are appropriate for the sarcoma/lymphoma study and they may be used for part of the analysis of the cohort studies data -- for example by the use of log-linear techniques for multidimensional categorical data analysis. However, the cohort design will permit the comparison of disease rates and thus allow direct estimates of relative risks. Such direct estimates will be made.

40) page 16 - Consider non-confounding covariates in analysis to increase precision

CDC staff have considered this suggestion and do not understand it. CDC would appreciate the opportunity to discuss this point with reviewer #7 if he/she can be identified.

B) Responses to Advisory Committee on Special Studies Relating to the Possible Long Term Health Effects of Phenoxy Herbicides and Contaminants (Ranch Hand Panel) Review Suggestions

1) page 2 - Importance of evaluating herbicide exposure differences among the Agent Orange study cohorts after review of military records

The advisory panel report states that "The strength of the difference between the two cohorts can only be ascertained after the service record analyses are complete. It is imperative.....that after the cohorts are identified, but prior to execution of the studies, an evaluation as to the specific strength and limitations of the studies be developed." CDC agrees that the usefulness of the Agent Orange study depends on separation of the the various cohorts in respect of herbicide exposure. CDC also agrees that much will be learned from the analysis of military records which is scheduled to be done by the AAOTF. However, it must be emphasized that CDC is of the opinion that it will not be in a position to specify that whatever exposure separation can be identified through the records review is "meaningful". That is, it will be impossible to be confident that the exposure separation represents an exposure difference which might a priori be considered enough to result in differences in long-term health. Moreover, it will not be possible to make quantitative estimates of the total true doses of herbicides and contaminants accumulated by the members of the various cohorts. CDC believes only that its sampling plan should identify groups of men who will differ to some degree in their accumulated exposure. It is possible (but thought unlikely) that the 50

battalions chosen will have identical exposure patterns. If there is no variance in the exposure estimates among the 50 battalions then CDC will propose that the Agent Orange study be reduced to a two cohort design, comprising a comparison of a cohort chosen from the 50 battalions with the currently proposed third cohort to be drawn from units stationed at places where no herbicides were used. If there is some variance in estimated exposure among the 50 battalions then the proposed choice of units from the top and bottom of the scale will maximize whatever exposure differential exists. CDC again emphasizes that the difference in true exposures will not become apparent after the military records review which is scheduled, and probably never will.

2) page 2 - Documentation of quality of records

The AAOTF will fully document the reasons for judging relevant records unacceptable.

3) page 2 - Do a special pilot study to compare personal recall with "Services Herbs" records to assess the completeness of the records

CDC is of the opinion that a pilot study of the "correlation" between the Services Herbs data set and personal recall would be of questionable usefulness. If a pilot study showed that veterans recalled applications which were not part of the current record, then a complete study of all Vietnam veterans who could have conceivably witnessed applications would be required to make the records "complete." On the other hand, if veterans did not remember applications of which "they should have been aware", it would not be justifiable to amend the records. However, CDC proposes that individual participants in the Agent Orange study be questioned about their perceptions of herbicide exposure and will incorporate this information in the analysis.

4) page 2 - More thought needed about weighting of exposures

CDC will explore the proposed and other weighting schemes after the records review is complete. The ability to do this will derive from the sampling procedure which CDC proposes -- a final weighting scheme does not need to be chosen until CDC has had an opportunity to assess the data assembled by the AAOTF (see OTA review response #1 for a description of CDC's revised sampling procedure).

5) page 2 - Is the ultimate exposure measure applicable to the individual veteran or the military unit?

The exposure criteria which are ultimately chosen will be applied to individuals. This was stated but not highlighted in the draft protocol and this lack of highlighting was the cause of confusion for several reviewers. The locations of individuals will be derived from unit records because there are no records which document the locations of individuals. However, there are records which specify whether or not an individual was assigned to a particular unit at a specified time. Thus the geographical location of an individual soldier assigned to a particular unit at a particular point in time will derive from the unit location at that time. All soldiers assigned to a particular unit at a particular time will be considered to have been at the same location.

6) page 2 - Comparability of location data on the HERBS tapes and in the unit records

The AAOTF states that location data from troop location and Herbs records are comparable; locations in both data sets were recorded using the Universal Transverse Mercator (UTM) system. However, some troop locations are recorded by geographical location (e.g., town names) and AAOTF will transcribe them to UTM.

7) page 2 - Consider using the individuals chosen for the Agent Orange study as the Vietnam service cohort for the Vietnam Experience study

CDC believes that the preferable way to select participants for the Vietnam Experience study is to sample records of individual veterans at the National Personnel Records Center. A team of AAOTF and CDC staff have recently completed a comprehensive assessment of procedures at the records center in St. Louis and have found that the system works very well. Unfortunately this sample selection approach will not work for the Agent Orange study. In addition, following this suggestion would make conduct of the Vietnam Experience study contingent on the selection of participants for the Agent Orange study and this could cause delay if difficulties are experienced in making that selection. Finally, the National Academy of Sciences advisory panel which reviewed the protocol prepared for the Veterans Administration before CDC received responsibility for designing and conducting these studies, strongly objected to a plan to use the same study to try to assess both the effects of Agent Orange and the experience of service in Vietnam. A similar suggestion was made by an individual reviewer of the Agent Orange Working Group Science Panel but the summary Panel review rejected the suggestion.

8) page 3 - Consider a staged questionnaire

This suggestion would have CDC reinterview certain participants, depending on their responses to questions in a preliminary questionnaire. This suggestion is motivated by a concern that "It is highly questionable if one can.....glean facts and characteristics of all diseases particularly when the condition and co-variates of interest include some of the most difficult to measure objectively". This suggestion has merit but in CDC's view it would be difficult to implement and control because it would be necessary to specially tailor interviews for each respondent needing reinterview. For this reason CDC proposes to limit in-depth questioning to those participants who take part in the examination phase. Moreover, CDC believes that the major difficulty will be in obtaining, during a telephone interview of reasonable length, information about potential confounders (co-variables) of disease-exposure relationships -- it is felt that it will be possible to gather most if not all important disease information in a relatively short interview. And in the absence of strong hypotheses it makes little sense to deal with all risk factors for a host of diseases when it is not known that Vietnam veterans are at increased risk. Effort should concentrate on determining the prevalence of various diseases. The sarcoma/lymphoma study provides an interesting contrast. Here there is a specific hypothesis at issue and the expenditure of time in gathering information about other suspect risk factors for the diseases seems appropriate. If definite hypotheses should arise from the cohort studies, it would be possible to perform "nested" case-control studies, using cases and controls identified from among the participants of the cohort studies.

9) page 3 - Guidelines for altering procedures after beginning principal investigations

Potential study participants will each be assigned to a relatively small number of groups, and groups will be "released" monthly for location, interview and examination by group. If procedures are changed in any way, the changes will apply only to those groups which have not yet been "released" at the time the changes are implemented. This approach will prevent the introduction of bias which could be caused by disproportionate application of the changed procedures to the difficult-to-locate.

10) page 3 - Prevention and assessment of recall and ascertainment bias

Attempts to prevent recall and ascertainment biases in the two cohort studies will include blinding of the interviewers and examiners with respect to study and cohort status of participants. In the Agent Orange study, the participants who are assigned to the "likely-exposed" and "likely not-exposed" cohorts will probably not know to which cohort they belong. It may or may not be possible to prevent those assigned to the third cohort from understanding the role of their data in the overall analysis; those who did not serve in

Vietnam who participate in the Vietnam Experience study will know that they did not serve in Vietnam. Even with the blinding in the Agent Orange study, recall bias may arise if the personal perceptions of participants regarding their herbicide exposure are well correlated with the exposure estimates made from military records. Where possible, attempts will be made during the examinations to validate responses given during interviews.

Ascertainment biases which could derive from sources external to communication with the participants should be controlled by taking care to achieve a high participation rate and through the use of information sources which should not be related to study group status. An example of the dilemmas which arise in this connection is the suggestion that CDC ask veterans service groups to help locate potential participants (see responses to OTA review suggestion #5). This suggestion has been questioned because of the undocumented possibility that group membership might be (strongly) related to cohort status.

11) page 3 - Extend examinations to include more sophisticated studies

Detailed immunological studies will be designed in consultation with non-CDC experts in the field; the same approach will be made for other areas of concern such as neuropsychological; see response #8 to OTA review for a discussion of chromosomal studies. However, it should be noted that CDC does retain skepticism about the use of tests which are not diagnostic or predictive of ill-health. Tissue and fluid samples will be stored for future use, but CDC does not plan to obtain fat biopsies.

12) page 4 - Give more extensive report of findings to participants and their physicians; do extensive work-up for definitive diagnosis

Full information about study findings will be provided to participants' physicians if requested by participants; to the extent reasonable, participants will be informed of findings by the study team. A certain amount of "as indicated" work-up for diagnosis will be made a part of the examination procedure. The draft protocol's statement on this issue was meant to indicate that there must be a limit to ad hoc work-up and that this limitation will be determined on the basis of what CDC's study team believes to be in the best interest of the veteran. For example, suppose a catheterization is indicated to arrive at a definitive diagnosis of some cardiac condition discovered (or suspected) as a result of the examination. A procedure such as this, which carries with it a non-trivial risk, should be done by the personal physician who will be responsible for treatment; most physicians prefer to perform their own diagnostic procedures and might therefore repeat them even if done by the study physicians.

13) page 4 - Comments on sarcoma/lymphoma case-control study

All comments, save one, have been addressed in the Office of Technology Assessment review responses. CDC concurs with the suggestion that primary liver cancer and nasopharyngeal and nasal cancer be added to the case group and has revised the protocol accordingly. In view of this addition, and because of the possibility of the addition of other cancers, the study has been renamed the Selected Cancers Case-Control Study in the revised protocol; however, the major focus of this study remains soft tissue sarcoma and lymphoma.

Responses to Individual Reviewer Suggestions

Written suggestions and comments of individual panel members have not been made available to CDC.

C) Responses to Science Panel, Agent Orange Working Group Review Suggestions

1) page 1 - Make use of information from VA's Agent Orange Registry and the Ranch Hand study

A table of diagnoses and complaints for men who are a part of the VA's registry has been reviewed recently. This tabulation was derived from an abstract of a VA presentation at the 1983 American Chemical Society meeting. The information available, which is not particularly detailed, does not provide CDC with any indications for a change in focus of its proposed studies. CDC has requested that the VA provide more detailed tabulations from the registry and from the VA's "Patient Treatment File" and will consider the data with regard to its' studies when received. CDC will also consider the results of the Ranch Hand study, and any other relevant investigations when they become available.

2) page 1 - Exposure index suggestions

See OTA (#s 1,2,18,26) and Ranch Hand Panel (#s 1,3,4,5) review responses.

3) page 1 - Staged questionnaires and examinations

See Ranch Hand Panel review response #8.

4) page 2 - Clearer delineation between pilot studies and principal investigation

The procedure which CDC outlined in the draft protocol does make a clear distinction between pilot and pretest procedures and the principal investigations, but as discussed in the draft protocol CDC does not propose doing a full and formal pilot study in the usual sense of the term. In the usual sense, doing a pilot study would imply that all procedures would be specified, and a small study completed under those specifications. CDC feels that this approach would be unwise for the cohort studies because so many of the proposed procedures are untried. If an untried procedure failed it might jeopardize the ability to make inferences about the feasibility of those procedures which followed the failed procedure. Perhaps the appointment of a steering committee which could monitor CDC's progress would allay some of the concern implicit in this suggestion.

5) page 2 - Criteria for defining soft tissue sarcomas varies among SEER centers

See Responses OTA Suggestion #15.

6) page 2 - Consider adding sarcoma cases from years prior to 1984

See response to OTA review suggestion #21.

7) page 3 - Re-evaluate herbicide exposure criteria after a review of military records

See response to Ranch Hand Panel review suggestion #1.

8) page 3 Fully explain the limitations of the proposed studies

CDC has attempted to inform interested parties that these studies have serious limitations; CDC has also pointed out that these limitations generally stem from the problem at hand and not from a lack of commitment or support. CDC will continue to try to convey this important message to interested parties.

Responses to Individual Reviewer Suggestions (only suggestions not covered above)

Review prepared by the National Institute of Environmental Health Sciences

9) page 1 - Select individuals for the Vietnam Experience Study so that the two cohorts are balanced for age, race, level of education, and region of country

This procedure is theoretically feasible but would add considerable labor to the process of participant selection and would cause delay in sample selection -- the sampling frame from which CDC must work is not stratified on these variables. Moreover, such a balancing would preclude a thorough check of the possibility that those who went to Vietnam differed from those who were stationed elsewhere -- i.e., it would interfere with evaluation of the "luck-of-the-draw" assumption of the Vietnam Experience study (see OTA review response #3 for a discussion of this issue). Also, if warranted, we can control for any residual differences amongst the cohorts in respect of these variables during the analysis.

10) page 1 - Include veterans of other services in Vietnam Experience study

It is believed that including veterans of the other services could destroy the comparability of of the two cohorts in respect of factors which influence health and which pre-existed service in Vietnam. For example, it is CDC's understanding that a large proportion of Marines volunteered for Vietnam service. Under this circumstance it would be difficult to obtain an appropriate comparison group of Marines. In addition, limiting the Vietnam Experience study to Army veterans would make the participants more like those who participate in the Agent Orange study (where limitation to Army veterans is necessitated by the quality of the military records) and this might confer an advantage at the time inferences are drawn from the data.

11) page 2 - Initial random selection of battalions does not guarantee that units with highest and lowest exposures will be chosen

CDC's proposed random sampling will not guarantee selection of units at the extremes of the exposure distribution (see response #1 to the OTA review for revised sampling plan). However, it should be remembered that the sample of 50 battalions will be drawn from a very small universe and it would be very unexpected if the sample does not include some units from near the top and bottom of the scale. CDC also emphasizes that none of the various schemes which have been proposed over the past few years will guarantee the selection of units at the extremes. Furthermore, unlike some proposed schemes, CDC's proposal will remove the subjectivity from the selection process. The only method for assured selection of the units at the extremes of the distribution would be to obtain location information for all units which served in Vietnam, an enormous task which would seriously delay the beginning of the study.

12) page 2 - Random selection of 1 day per week for troop location could result in misclassification of exposure

See OTA review for response (#1) to similar criticism.

13) page 3 - Other sarcoma studies are planned or ongoing -- avoid duplication of effort in sarcoma/lymphoma study

See OTA review response (#21) to similar criticism.

14) page 4 - Describe how results of pilot studies will affect decisions

The results of the various pretests and pilot studies will be used to decide how main study procedures should be modified. For minor issues, the changes will be made as an administrative matter by CDC. For more important matters, CDC will consult with its steering committee and with OTA. An example of a minor issue would be changes in the wording of questions in the interview or the addition or deletion of tests to the examinations. Examples of major issues would include the use a different sampling scheme for one of the studies or a recommendation to abandon one or more of the studies because of very low participation.

15) page 4 - Is exclusive use of Army veterans acceptable?

See OTA review response to similar question (#24).

Review prepared by Office of Pesticides and Toxic Substances, Environmental Protection Agency

16) page 2 - Use VA publications to estimate the number of Vietnam veterans who reside in the areas served by the SEER centers

An estimate was made by OTA staff who calculated a Vietnam service prevalence of 8% among men in the age range which CDC proposes to include in the sarcoma/lymphoma study. See OTA review response #13 for related comments.

17) page 2 - Consider identifying potential participants for the Agent Orange study from the VA Agent Orange Registry

This suggestion would have CDC identify "likely-to-be-exposed" units on the basis of information in the VA's registry, since "It is expected that some military units would be likely to be reflected as having multiple claimants....from the same units and that these units were within close proximity to aerial spray missions. Similarly, the units selected as unexposed....should have fewer claimants." CDC does not agree with this suggestion as it would result in a self-selected sample that would seriously affect the interpretability of the study data.

18) page 3 - Consider measuring dioxin residues by objective analytic procedures

An objective and valid measurement of individual dioxin exposure which occurred in Vietnam would be invaluable. To CDC's knowledge, no technique to make such a measurement is available. Even the development of a simple method to assay current body burdens in large numbers of individuals would not solve this problem. The half-life of dioxin in humans is unknown and if short might prevent making inferences about exposures which occurred 15 years ago from present day levels. Recent exposures, even those to quantities much lower than those which might have been encountered in Vietnam, would overshadow the residual from Vietnam. However, if mean body burden levels in the "exposed" cohorts were higher than those in the "unexposed" cohorts some degree of confirmation of the classification of veterans might be accomplished.

19) page 3 - Rationale for assessing unit herbicide exposures by sampling locations for 1 day per week

See OTA review reaction #1 for proposed changes in response to this and similar criticisms.

20) page 4 - Proposed selection process for Agent Orange study does not guarantee selection of most highly exposed individuals

See response to similar criticism made by National Institute of Environmental Health Sciences (#11 of Agent Orange Working Group review).

21) page 4 - One-time physical examination and interview deficient because earlier health effects may have resolved and are now undetectable, currently existing health effects may be subclinical, or health effects may develop at a later time.

The mortality and (parts of the) interview phases of CDC's proposed studies are by nature historical and address the first concern as adequately as is possible. By definition, the examinations and laboratory tests cannot detect problems that are present only at "subclinical" or "sub-laboratory" levels. CDC's proposal to do long-term follow-up only for mortality does not preclude further interviews and examinations at later times, if deemed necessary. Such decisions can be more appropriately made after the proposed studies are completed.

22) page 5 - Several suggestions for the Sarcoma/Lymphoma study

See OTA review responses #s 13,14,21 for reactions to similar suggestions.

23) page 6 Consider using Agent Orange study participants as a part of the Vietnam Experience study

See Ranch Hand Panel review response #7.

24) page 6 - Consider using the VA Agent Orange registry or VA Patient Treatment File to construct case-control studies for specific diseases

Where specific hypotheses about rare diseases are available (for example soft tissue sarcoma), case-control studies have much to recommend them. Unfortunately, as noted repeatedly in the draft protocol, there is a dearth of specific hypotheses. Even if hypotheses were available CDC would be reluctant to derive study subjects from a file such as the VA Agent Orange registry because of fear of selection bias.

25) page 7 - Problems detecting reproductive effects in male veterans -- consider investigating reproductive histories of spouses.

See OTA review response #7 for comment on similar suggestion.

26) page 7 - Consider study of "chemical unit sprayers"

This suggestion has been made since "....this group is the only cohort which is most likely to demonstrate physical and sub-clinical findings." While there may be some truth to the notion behind this statement, those veterans who were assigned to the chemical units numbered only about 1000. The relevance of findings in this small group to the vast majority of Vietnam veterans is questionable. There is a separate concern that the "chemical units" were apparently exposed to many chemicals other than herbicides. However, as the EPA reviewers noted, study of this group would not preclude the study of other Vietnam veterans. CDC would consider the addition of this group to its study, if similar sentiment were expressed by other reviewers, and if appropriate resources were made available.

Review prepared by Walter Reed Institute of Research

27) pages 1&2 - Several comments regarding weaknesses of Agent Orange exposure estimation proposal

Most of these criticisms have been spoken to by CDC elsewhere in response to the AOWG summary review, the OTA review and the Ranch Hand Panel review. However, this reviewer emphasizes problems of misclassification. The effects of misclassification have not been specifically dealt with elsewhere, even though concern about its effects are implicit in all the discussions. The reviewer mentions several aspects of herbicide exposure estimation which could result in the truly exposed being classified, for study purposes, as unexposed and in the truly unexposed being classified as exposed. If the misclassification were random then, as the reviewer states, any true difference in health status between the exposed and non-exposed would be

minimized and this could be detrimental to veterans. If the misclassification were not random, then the true difference could appear to be accentuated, reduced or even reversed. The reviewer suggests that CDC should investigate the cumulative effects on study power of a variety of sources of misclassification (presumably on the assumption that the misclassification would be random). There is no "gold standard" to which any method of exposure estimation can be compared, and unfortunately any formal examination of the effects of misclassification requires a "gold standard." It may be noted that the inability to refer CDC's proposed method of exposure estimation to a "gold standard" would apply to any other method of estimation which relies on the use of military unit records to make the estimates. Again, it needs to be said that CDC is aware that the Agent Orange study is imperfect and has tried to convey that opinion to veterans groups and the Congress. However, CDC notes that the presence of random misclassification in exposure estimates is not necessarily an adequate reason for not conducting the study. If health effects are strong enough, they would be discovered by the study, albeit underestimated. In addition, the current state of ignorance about the health of Vietnam veterans may be viewed as detrimental to veterans. The proposed studies will surely shed some light on this issue of great concern to veterans.

Review prepared by the Office of the Assistant Secretary of Defense (Health Affairs)

28. pages 1-3 Several criticisms of CDC's proposed Agent Orange exposure estimation scheme

This review expresses some "very serious concerns" about CDC's proposed procedures to select individuals for the Agent Orange study. The reviewer apparently takes issue with: 1) the random selection of 50 battalions from among those serving in III corps, and 2) ranking the 50 units by an estimate of exposure derived from a 1 day per week sampling of unit locations. These criticisms have been addressed in response to similar criticisms made by OTA and Ranch Hand Panel reviewers and by other AOWG reviewers. Briefly, the random selection does not guarantee selection of units from the extremes of the exposure distribution but it would result in an objective and describable selection process. Furthermore, the sample chosen would represent a large fraction of the universe and this would make it highly likely that some units near the top and some near the bottom would be chosen. As noted in CDC's response #1 to the OTA review, the problems which would attend sampling unit locations one day per week are no longer an issue since the AAOTF has determined that it will be able to provide unit location data for all days during 1967-1968 for each of the 50 selected units within a reasonable time.

As an alternative to the random selection of 50 units the reviewer offers what appears to be an essentially subjective process. For the most likely exposed group CDC would ask that the AAOTF find the ".....50 battalions who by map comparison to the Herbs tape plots for CY 1967 and CY 1968 operated in very heavily sprayed Ranch Hand areas." The key here is how this "map comparison" is done. One way would be to make the "map comparison" using location data abstracted (perhaps on a sampling basis) from records of units (also possibly chosen by a scientific sampling) which were operating in III Corps in 1967-1968. If this were done then the scheme would be in principle no different than that proposed by CDC. Indeed, if it were done using all units operating in III Corps in 1967-1968 the process would be obviously preferable to CDC's plan of sampling 50 battalions. However, a full census would cause delay in beginning the study. On the other hand, if the units are selected by some subjective (and non-describable) system, CDC would find the process unacceptable. CDC cannot be placed in the position of defending its study to critics who would, under such circumstances, surely imply that the study is invalid because the sample was chosen for CDC using subjective processes.

29) page 4 - Do some tests to learn more about the distribution and environmental fate of herbicides when applied from fixed-wing aircraft, helicopters, trucks, etc.

CDC would welcome the results of any tests which could help it to sharpen the exposure scales; tests for present-day dioxin levels in Vietnamese soil might also be useful. However, such tests are not within CDC's capability. Perhaps the interagency Agent Orange Working Group can arrange to have such experiments performed. It must be noted that it would be necessary to have them completed fairly soon if they are to be of any utility to CDC in its choice of individuals for the study.

Review prepared by the Dioxin Activity, National Institute for Occupational Safety and Health

30) page 1 - It is essential that histological criteria - not ICD codes - be used to select soft tissue sarcoma cases for the case-control study

See OTA review responses #s 13 & 15.

31) page 1 - Use colon cancer cases as controls

See response to OTA suggestion (#14) to include a diseased control group

32) page 2 - "Minor Detailed Comments"

The revised protocol has corrected the errors noted in this section of this review.

D) Responses to Centers for Disease Control (CDC) Ad Hoc Panel Review Suggestions

1) page 1 - Make Agent Orange exposure estimates for individual veterans

Each member of the first 2 cohorts of the Agent Orange study will be assigned an individual exposure score. This issue was discussed in the responses to the Ranch Hand Panel review (#5).

2) page 1 - Verify the accuracy of the Herbs tape data

As was noted in the draft protocol, the National Academy of Sciences has reported a relatively limited accuracy check which made use of aerial photographs to compare areas of defoliation with spray missions as documented on the Herbs records. The results of this analysis are encouraging, but have been criticized as being derived from data which are unrepresentative of the general situation in Vietnam. It is understood that the analysis was done for an area of flat terrain and that the results may not be generalizable to hilly or mountainous areas. CDC has requested that a more generalized evaluation be made of the accuracy of the Herbs tape data using the aerial photograph comparison approach.

3) page 2 - Power of Sarcoma/Lymphoma study based on expected prevalence of Vietnam service, not prevalence of Agent Orange exposure

See response to similar criticism in the OTA review (#13).

4) page 2 - Make use of Ranch Hand study data on the validity of herbicide exposure data

The Ranch Hand study is a health study of men who were exposed to herbicides by virtue of the fact that they flew the aircraft from which spraying was done; the control group comprises the crew of similar aircraft which were used for other purposes (e.g., supply). The Ranch Hand study procedures do not include a collection of any data which would permit an assessment of the accuracy of the Herbs records or exposure of ground troops in the path of the spraying.

5) page 2 - Construct third cohort for Agent Orange study from among combat troops which served in non-sprayed areas

See OTA review response #2.

6) page 2 - Is the "luck-of-the-draw" assumption for the Vietnam Experience study valid?

See response to similar question in OTA review (#3).

7) page 2 - Make use of the Agent Orange study cohorts as the Vietnam cohort in the Vietnam Experience study

See response to similar suggestion in the Ranch Hand Panel review (#7).

8) page 3 - Collect as much objective information as is possible.

The rationale for this suggestion, as stated by an individual CDC reviewer, follows: "...I would suggest to the investigators that they adopt the principle of 'if the information is potentially useful, then get it.' While this principle is generally applicable, these studies would seem to require its adoption even more than is generally the case. I suspect the sample sizes of each cohort (6,000 interview, 2,000 lab) will prove to be insufficient for answering all of the questions that will have been posed and will be suggested by the data."

The CDC study team appreciates the spirit of this suggestion. What epidemiologist or statistician hasn't wanted a bigger sample to support one more stratification of the data; or information on the potential confounding variable posed by the critic as the crucial missing factor in the analysis. However, the team must balance a desire to do a more all-encompassing study, the desire to gather all possibly useful data on a much larger sample, with the desire to complete studies within a reasonable time. The interview phase of the proposed studies will involve a rather abbreviated questionnaire focused on gathering demographic, morbidity and military data, without a major effort to collect much in the way of information about potentially confounding variables. The examination phase will "fill out" the interview and will involve gathering extensive history, physical and laboratory data, although on a smaller sample. The size of the examination sample and the extent of the data gathered should allow a quite comprehensive assessment of relatively common health problems. The interview phase should provide reasonably good estimates of prevalence for rarer diseases but may require follow-up to sort out the effects of potential confounding factors. In short, the CDC study team believes that it would be best to proceed with a study which can be completed in 4 or so years, a study which will provide reasonably good estimates of disease prevalence rates, even though it may not allow for a detailed sorting out of causal nuances. Presently, there is very little information available on the health of Vietnam veterans. Four years is a long time for interested veterans to wait. And it is already 3 years since the Congress mandated that health studies should be done.

Comments on the issue of the depth of the proposed interview have also been made in response to the Ranch Hand Panel review (#8).

9) page 3 - Because sample size is small, spare no effort to get high participation rate

Every reasonable effort will be made to achieve a high participation rate, but it should be understood that a rate much above 70% is probably unattainable. As a part of this effort, CDC's budget request was made sufficient to pay the veterans a generous stipend to participate in the examination phase.

10) page 3 - Collection of good information on illicit drug use very important

There will be consultations with experts in the field of drug abuse to try to define the best ways to gather data on illicit drug use. The study team has applied for a Certificate of Confidentiality which would permit a pledge to participants that information collected from them will be held in complete confidence. It is anticipated that this pledge should be of some help. However, the team is not sanguine that there can be any high degree of assurance that fully valid data will be gathered.

11) page 3 - Include older aged cases in the sarcoma/lymphoma case-control study to better identify key risk factors

The support for this study is to be provided for the purpose of learning about what risks may be associated with service in Vietnam and Agent Orange. Therefore, the study team would be reluctant to add substantially to the study solely for the purpose of identifying risk factors for the cancers which might or might not apply to cases in the age range of Vietnam veterans. Perhaps such information might derive from other on-going studies of sarcomas and lymphomas. However, the revised protocol does call for addition of men with birth dates 1929-1932, men who conceivably could have served in Vietnam, and this addition substantially increases the number of cases available.

Responses to Individual Reviewer Suggestions (only those not addressed above)

Review prepared by the Division of Bacterial Diseases, Center for Infectious Diseases

12) page 2 - Why are nerve conduction velocity studies not a part of the examination procedures?

Nerve conduction velocities will be measured during the Agent Orange study examinations.

APPENDIX A

OFFICE OF TECHNOLOGY ASSESSMENT REVIEW

Office of Technology Assessment
Review of

Centers for Disease Control
Protocols for Epidemiologic Studies of the Health of Vietnam Veterans

July 1983

Office of Technology Assessment

AGENT ORANGE STUDY PROTOCOL REVIEW
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Office of Technology Assessment

Review of

Centers for Disease Control

Protocols for Epidemiologic Studies of the

Health of Vietnam Veterans

June 1983

INTRODUCTION

The Centers for Disease Control (CDC) draft Protocols for Epidemiologic Studies of the Health of Vietnam Veterans (hereafter "protocols") is a well constructed plan for conducting three studies to inquire into health effects possibly associated with exposure to Agent Orange and other aspects of service in Vietnam. The protocols reflect careful attention to the processes of conducting large and complicated studies and discuss the power of the studies to detect possibly increased frequencies of diseases and conditions among Vietnam veterans.

The Office of Technology Assessment (OTA) is impressed not only with the quality of the protocols but also with the manner in which CDC has developed the protocols and arranged for their review. In addition to governmental agencies, CDC has solicited advice and review from veterans organizations. The result is a superior product and an apparent sense that CDC is open to advice and critique. The latter is very important in that it will contribute to better cooperation and participation during the conduct of the study and consideration of its results.

An indication of the thoroughness of CDC's effort is the protocols' discussion

of possible problems and pitfalls in the execution of the study. In many cases, CDC does not spell out a rememdy for things that might go wrong, but it acknowledges the possibility of having to alter plans to accommodate circumstances. The protocol designers will be going into the study with their eyes open, and that is most encouraging.

The protocols describe 3 studies:

1. Cohort Study of the Long-Term Health Effects of Exposure to Herbicides in Vietnam (At the OTA Advisory Panel meeting to review the protocols, Dr. D. Erickson from CDC clarified that "Herbicides" in the title of the study refers specifically to Agent Orange);
2. Cohort Study of the Long-Term Health Effects of Military Service in Vietnam; and
3. Case-Control Study to Determine the Risks for Soft-Tissue Sarcomas and Lymphomas Among Vietnam Veterans.

Many associations between Agent Orange exposure or Vietnam service and health effects have been suggested. However, few of the suggested associations have been studied and there are few associations to be tested in the proposed studies. In the absence of testable hypotheses, the first two studies are designed to generate hypothesis. They will look at veterans' health and causes of death to see if there are excesses in the Agent Orange exposed population and the Vietnam veteran population as compared to other groups of veterans. One association between health effects and herbicide exposure that has been demostrated is excess soft tissue sarcomas and lymphomas among occupationally exposed workers. The hypothesis that Vietnam veterans exposed to Agent Orange are at increased risk for those cancers will be tested by the third study.

This review discusses each of the three studies. Those discussions are followed by comments about aspects of the 1st and 2nd studies that are similar. OTA's plan for conducting its Congressionally mandated monitoring of the studies'

execution is briefly mentioned. Appended to the report are specific written comments made by members of the OTA Advisory Panel, which met on June 24, 1983. The panel meeting and this review benefitted from open communications between CDC and OTA and the presence at the meeting of Drs. Erickson and Layde from CDC. They provided clarification and amplification of aspects of the study in response to questions and comments from OTA Advisory Panel members and OTA staff.

COHORT STUDY OF THE LONG-TERM HEALTH EFFECTS OF

EXPOSURE TO HERBICIDES IN VIETNAM

("AGENT ORANGE STUDY")

Description of the Study.

The Agent Orange Study will compare three cohorts of 6,000 men each: 1) troops who served in combat areas and who were located near areas of recorded uses of Agent Orange; 2) troops who served in combat areas and who were not near recorded uses of Agent Orange; and 3) troops who did not serve in combat areas and who were not exposed to Agent Orange. Given the close relationship between combat and use of herbicides, there is and always will be some uncertainty about the exposure status of combat troops. In particular, combat troops placed in the second cohort may actually have been exposed to Agent Orange.

Both mortality and morbidity will be studied. The mortality analysis will be based on reviewing death certificates and medical records (see Mortality Analysis in this review). Morbidity will be assessed through a health and exposure interview of all participants and a medical examination of 2,000 veterans from each cohort.

OTA's March 1983 review of CDC's outline for these studies raised the point that inclusion of the third cohort will increase the size and cost of the study and asked that CDC estimate the magnitude of the problem of misclassification of veterans between cohorts 1 and 2 before a final decision was made to include the third cohort. The protocol does not specifically discuss the magnitude of the misclassification problem. However, CDC remarks "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"

(p. 16). Inclusion of the third cohort provides assurance that a cohort of non-exposed individuals is included in the study.

The protocol does discuss the difficulties of interpreting possibly different health outcomes between cohorts 2 and 3, both of which are "controls." For instance, if cohorts 1 and 2 are found to have similar disease risks in comparison to one another, but elevated in comparison to the third cohort, it will be impossible to say whether the lack of difference between cohorts 1 and 2 is due to exposure misclassification or if the difference between those two and the third cohort reflects a difference between combat veterans (cohorts 1 and 2) and non-combat veterans (cohort 3). Of course, if the first cohort is found to have higher disease risks than either of the other two, the inference that exposure to Agent Orange increases health risks will be clear (p. 73).

Selection of Veterans for Inclusion in Cohorts 1 and 2.

The Agent Orange Study will consider only veterans of the United States Army who were one-term enlistees or draftees and who served one tour of duty in the III Corps area of Vietnam during the period 1967 through 1968. These limitations reduce the problems of deciding whether to classify a veteran as exposed or not exposed. After considering inclusion of veterans of the United States Marine Corps, CDC has now opted to exclude Marine veterans from the study. The Marines served in different areas of Vietnam, and more of them were volunteers as contrasted to the mix of draftees and volunteers in the Army.

According to the Army Agent Orange Task Force (AAOTF), about 110 to 120 Army combat battalions were stationed in III Corps during the 104 weeks of 1967 through 1968. The records of those battalions will be reviewed to select those that are most complete, and 50 battalions (250 companies) will be selected at random from those with acceptable records. The next step will be to go through the records and

establish the location of each of the 250 companies on one randomly chosen day for each of the 104 weeks.

The company locations will be matched with records of herbicide use to establish how near each company was to an herbicide use during each week. Herbicide exposures may have resulted from Ranch Hand spray missions or applications from helicopters, spray trucks, or backpacks. Although the Ranch Hand records are considered the most complete, they have not been extensively reviewed for accuracy, according to CDC, and the records of other uses are probably poorer. Despite those reservations about the records of herbicide use, those records are all that exist, and they must be used in the effort to establish proximity to herbicide use.

Three methods will be used to rank companies on the basis of exposure. The first will assign a weight to distance and time from an herbicide use on a geometric scheme; the second will use linear weights; the third will weigh equally all uses within 3 days and 2 kilometers of the company location. The first system will accord greater differential weight to closer uses than will the second. The third is a "yes/no" classification scheme.

The total exposures will be summed for the 104 weeks, and companies will be placed in an exposure continuum. It is likely that all three ranking systems, geometric, linear, and yes/no, will produce the same results and that a company ranked at the top in one scheme will also be ranked at the top in the other two. In that case, about 50 companies from the top of the rankings will be selected for cohort 1 and 50 companies from the bottom will be selected for cohort 2. In the event that the three schemes produce different rankings, cohort 1 will be made up of about 17 companies from the top of each of the three exposure indices; cohort 2 will be composed of an equal number of companies from the bottom of the indices.

Individuals will be selected for inclusion into the cohorts by examining company records to find soldiers who were enlisted men, who were drafted or one-term

volunteers, who served with a selected company for all 12 months in Vietnam during the 1967 through 1968 period, and who were present for duty with the company at least 9 of the 12 months. CDC estimates that 55 companies, each providing 150 individuals who meet the criteria, will be sufficient to complete cohorts 1 and 2.

Comments on the Selection of Cohorts 1 and 2.

CDC's decision to sample on one random day each week is motivated by a desire to reduce the number of records that have to be reviewed to decide which companies are likely to have been exposed and not exposed. [Even so, according to CDC (personal communication, Dr. D. Erickson, June 24, 1983), the AAOTF will require one year to abstract the records necessary to classfiy the companies on a one day a week sampling scheme.]

There is a possibility that one day a week sampling will misclassify some companies. If a company was very near an herbicide use on Sunday, and the random day for CDC to determine its location that week was Saturday, 6 days would have passed since the exposure. That exposure would receive a lower score than if the sampling day were the same as the exposure day. If this were to happen several times in the 104 weeks, a company that was highly exposed might be classified the same as companies that were less exposed.

After the individual soldiers are selected, the daily location of the selected companies will be determined for all days, and, in fact, a more rigorous exposure rating, based on daily locations and herbicide uses will be calculated. However, according to CDC, those daily locations will not be available until about 2 or 2½ years after the study begins. Finding out that late in the study that the one day a week sampling for locations had produced serious misclassifications would be very detrimental to the study.

OTA would suggest two possible mechanisms to check that CDC's one day a week sample does not cause significant misclassification. First, CDC might sample "day

pairs". In this procedure, CDC would select, as is proposed, a random day in every week of the 104 weeks of 1967 through 1968. It would analyze those data by the three methods and rank the 250 companies on the basis of exposure. Then, for a subset of those 250 companies, it would select another day, perhaps either the day before or the day after the random day already analyzed, and repeat the ranking procedure. If the rankings remain the same, or nearly so, it would then appear that the one day a week random sampling had not introduced any bias into the exposure rankings. As a second check on the effects of the one day a week sampling scheme, after the top and bottom fifty companies are selected, CDC might do a day-by-day comparison among 2 or 3 companies from the top 50, 2 or 3 from the bottom 50, and 2 or 3 from the companies in the middle of the exposure range.

Selection of Veterans for Cohort 3.

The third cohort will be selected from veterans who resemble those in cohorts 1 and 2 as much as possible, but who served in areas of Vietnam in which no herbicide was used. The AAOTF has suggested that Cam Ranh Bay or Vung Tau might be such areas.

Comments on Cohort Selection.

CDC acknowledges that records about herbicide use and consequent exposure are limited. That cannot be changed. At the same time, CDC is using the available information in a workmanlike manner and in a manner that is easy to review and comment upon. The approach they have chosen may well be the best that can be taken.

Although it appears unlikely that the methods chosen will not allow some separation between exposed and non-exposed veterans, that possibility must be kept in mind. In other words, it is still possible that studying associations between health effects and Agent Orange exposure may not be possible because the records will not provide information for meaningful exposure classification. The protocol shows that CDC is aware of the problems in deciding about exposure status and

provides assurance about the ability of the CDC to make appropriate decisions as the study goes along.

The protocol gives little attention to the selection of cohort 3. It is important, however, that every effort be made to fill that cohort with veterans who resemble as much as possible individuals in the other two cohorts.

COHORT STUDY OF THE LONG-TERM HEALTH EFFECTS OF

MILITARY SERVICE IN VIETNAM

("VIETNAM EXPERIENCE STUDY")

Description of the Study

The health status of two cohorts of non-officer Army veterans will be compared in this study: one cohort will be Vietnam veterans; the other veterans who served in the Army during the same time period but not in Vietnam. Six thousand men will be included in each cohort. The National Personnel Records Center in St. Louis, which houses personnel files for all discharged service persons (except the living retired and those in the active reserves), will be used to identify individuals to be included in the cohorts. Men who served during the period 1966-1971 will be eligible for the Vietnam service cohort, and they will be chosen in proportion to U.S. troop strength in Vietnam during those years. The distribution of period of service will be equivalent for the non-Vietnam cohort. Those serving only in the U.S. and Vietnam will be included in the Vietnam cohort. The non-Vietnam cohort will comprise three equal sized groups: individuals who served only in the continental U.S.; individuals who served in the U.S. and Europe; and individuals who served in the U.S. and Korea. Based on a sample of 101 Army records drawn from the St. Louis Center, CDC has determined that using that approach is a feasible way to select cohort members with little wasted effort.

The basic elements of the study are identical to the elements of the Agent Orange study: a mortality analysis from death certificates and supporting documentation for those who have already died (it is proposed to repeat the mortality analysis at 5-year intervals to keep track of causes of death in the cohorts); a health and exposure questionnaire for all participants; and a medical

examination including laboratory tests for a random sample of 2,000 participants.

Limitations and Difficulties

The study designers are entering into the Vietnam experience study with full appreciation of its limitations and difficulties. The lack of firm hypotheses about what specific health effects might be caused by having served in Vietnam, and the wide range of complaints voiced by veterans make designing a relevant questionnaire and examination a great challenge. Considering the enormous complexity of the Vietnam experience, the possibility of identifying long term health outcomes may be remote. As yet unrecognized conditions may be most likely found in investigations of psycho-social characteristics. Almost by definition these outcomes are likely to be vague and difficult to relate specifically to service in Vietnam.

Comments

Despite the limitations of the Vietnam experience study and the inevitable difficulties that will accompany interpretation of the study results, the protocol designers present a clear and convincing rationale for carrying out the study. OTA concurs with their reasoning and with their choice of study design.

The Vietnam Experience Study is based on the premise that, once classified into a particular military occupational specialty, whether an individual went to Vietnam or served elsewhere was simply a matter of probability or luck. This means that soldiers were not "selected" by one or a set of characteristics for Vietnam service. If the "luck of the draw" argument does not hold, and there was some explicit or implicit selection for Vietnam service, the preexisting differences between those who did and did not go to Vietnam could be related to differences in their health status today. As CDC recognizes, there is little hard evidence one way or the other on which to base belief in the luck of the draw. It is basically taken

on faith.

One characteristic of veterans about which something is know is which states they lived in at the time of their induction or enlistment in the Army. Different geographic areas of the country are associated with difference socioeconomic status, and industrial and agricultural activities. There are some suggestions that the proportion of soldiers that went to Vietnam varied from state to state. If that is the case, it will suggest that the luck of the draw was not the only factor that decided where a soldier served. Furthermore, it will require CDC to consider factors other than service in Vietnam in its analysis of this study.

The protocol designers state that they may make multiple comparisons of the Vietnam cohort against subgroups of the controls. As possibilities, they mention comparing foreign versus U.S. experience and Korean versus European service to provide contrasts between different types of foreign environments. It appears unwise to diffuse the focus of the study with these multiple comparisons, particularly without specific reasons for doing so. Such comparisons would be difficult to interpret and would be of lesser power than comparisons of the two entire cohorts. OTA suggests that the comparison be focused on the Vietnam experience.

FEATURES COMMON TO THE AGENT ORANGE AND VIETNAM EXPERIENCE STUDIES

Power of the Studies

The Agent Orange and Vietnam Experience studies will have high power (sensitivity) to detect a 2-fold increase in the risk for health outcomes that occur in the control population at a rate of about 0.5%, for outcomes based on the questionnaire phase. For the medical, psychological and laboratory phases, the studies will have high power to detect 2-fold increases in outcomes that occur at the rate of 1.5-2.0% in the control population. For outcomes occurring more frequently, and for greater increases, the studies will have coorespondingly greater power. In comparison to most cohort studies that have been done, these studies are very powerful due to their large size. Even so, as CDC recognizes, the cohort design is not well-suited to detecting rare effects or those which occur at only slightly increased frequencies in the exposed group.

The disease frequencies of 0.5 to 2.0 percent used in these power calculations are not derived from specified hypotheses about any disease conditions which are suggested by theory or prior observation as being increased in these populations of veterans. Conditions which occur in such frequencies in young and early middle aged males are common allergies and mild upper respiratory infections. No observations suggest that these or other common conditions are doubled in frequency in association with herbicide exposure 20 years previously. The power calculations are illustrative of disease effects that the proposed studies are capable of detecting, not of effects expected on the basis of either theoretical or empirical considerations. In the absence of such expectations, this major research effort cannot be considered justified in terms ordinarily used by scientific review bodies. Approval of these protocols is taken to imply that, if study of the health

experience of these veterans is justified on other than only scientific basis, then the proposed research plans are appropriate for such studies.

Recruitment and Participation

As part of the selection of individuals for cohorts, the AAOTF will supply CDC with the veteran's service number, social security number, his address at the time of discharge, and the name and address of one parent and one sibling if available. CDC expects that the Internal Revenue Service will be the major actor in locating veterans, and this will be facilitated by there being a Social Security Number for almost all veterans. The Social Security Number and name will also be transmitted to the Social Security Administration and the Veterans Administration. The Social Security Administration can determine if the person is deceased, and, if not, whether he has recently paid social security taxes and who his employer is. The Veterans Administration can also veryify the fact of death from its records of paid death benefits.

The above procedure is being assessed by a pretest on a group of 840 names of veterans obtained from the AAOTF. If the results of that test are encouraging, CDC expects to do no more testing of the methods for locating veterans before moving on to a pilot study (p. 59). On the other hand, serious difficulty in locating veterans may force CDC to employ more expensive methods, involving credit bureaus and contacts with neighbors at last known addresses, to locate veterans. Finally, if no method appears to offer promise of locating veterans for the cohorts, a complete rethinking of the Agent Orange and Vietnam experience studies may be necessary.

There is no way to carry out the Agent Orange study if the cohort selection systems fail, because the location of veterans from particular companies is essential. The Vietnam experience study could, however, be done by using random

digit dialing to locate Vietnam theater and Vietnam era veterans, but that approach would cost a great deal of money to identify sufficient numbers of veterans.

CDC describes a pilot study to determine the rates of locating veterans for the Agent Orange study and to determine their rates of participation. Ten companies will be selected at random from the 110 to 120 battalions that served in III Corps, and 40 men will be randomly selected from each of the 10 companies. Those 400 names will be "run through" the location process and the located veterans contacted for interviews. If that pilot test is successful, (CDC does not specify what will constitute success), CDC will go ahead with the interviews of the study cohorts (p. 61).

In the outline for the study, CDC specified that 70 to 75 percent of cohort members would have to be located and participate in the questionnaire phase of the pilot study to justify continuation of the study as planned. Evidently, CDC still requires that participation rate because it will select about 150 veterans from each of about 55 companies (8,250 men) for each of the three Agent Orange study cohorts. If 70 percent participate, that will result in 6,188 men in each cohort.

To participate in the interview phase of the studies, which is a prerequisite for the examination phase, the veteran must have access to a telephone. CDC estimates that 5 percent of households in the United States do not have telephones, but the percentage varies with income and is higher among lower economic groups. Not having a phone where he lives does not mean a veteran cannot participate in the interview phase; it may be possible to contact him at another phone. If phone contacts fail to achieve a 70 percent participation rate, CDC will attempt to reach additional veterans through personal interviews. However, if 70 percent participation is achieved, no such efforts will be made.

CDC acknowledges that it is venturing into the unknown and is uncertain about which factors will induce or inhibit high participation rates. The protocols are

strengthened by CDC's plans to employ pilot studies to answer questions about what will contribute to high participation rates instead of plunging ahead into the main study without obtaining that information.

CDC has ruled out conducting the medical examination in VA or CDC facilities. Beyond that, CDC has made no decision about the location of the examinations except to say that it favors conducting all of them in one or two centers. The protocol states that it is unknown whether a long plane trip would be an incentive or disincentive for participation. Furthermore, the effects of offering compensation to participants will be examined in the pilot test.

Comments on Recruitment and Participation.

CDC sees locating veterans as a difficult task. At least 15 years have passed since the veterans to be included in the study were discharged, and their addresses are, therefore, 15 years old.

A veterans service organization represented on the OTA Advisory Panel made a suggestion about CDC's location and recruitment efforts: In addition to the IRS, CDC might also contact veterans organizations and ask them to look among their membership rolls for addresses of veterans. There may be some legal restrictions on the extent of veterans organizations' releasing names and addresses, and that is being investigated by the organiation.

It will be important for CDC to record reasons for not enrolling veterans in the studies. For instance, veterans without telephones will probably be less likely to be interviewed. Finding that the percentages of veterans who do not participate for various reasons are similar among different cohorts will reduce concern about differential participation contributing to a bias in the results.

At least 15,000 veterans are party to lawsuits brought against manufacturers of Agent Orange or its components. On a random basis, the number of veteran plantiffs expected to be invited to participate in the studies should be equal to their

percentage in the population of Vietnam veterans (about 15,000/2,800,000 = 0.5 percent). Therefore, the number of plantiffs in the study should be 0.5 percent of 30,000 or about 160 total in all cohorts and about 32 in each cohort. CDC proposes that whether or not a veteran is a plantiff will have no effect on his being invited to participate. This is a reasonable procedure.

Mortality Analysis

Some concerns were raised by OTA Advisory Panel members about possible difficulties that might be introduced in the mortality analysis by CDC's supplementing death certificate information with hospital and other medical records. Since those records will be available for only some of the deaths that occur, some bias might be introduced into the analysis. If such information is collected, it was suggested that an analysis based only on death certificates also be carried out.

Questionnaire and Medical Examination

The questionnaire and medical examination are presented only in outline form with little discussion in the protocol. CDC will, with the addition of expert consultants, develop those instruments in the next few months.

The questionnaire and medical examination sketched out in the protocols are improvements over those that appeared in the outline except for a few specifics. For instance, the questionnaire in the outline included a query about hobbies, which are associated with sometimes significant exposures to hazardous chemicals. That question was not present in the protocol, but CDC acknowledged that its deletion was an oversight, and that it will be restored.

It is impossible to comment further on the questionnaire and examination until

more details are available. OTA is willing to circulate drafts of the questionnaire and examination to appropriate members of the Advisory Panel for comment if CDC desires. However, OTA would prefer to wait until after the pilot study of the questionnaire is complete before reviewing it. At that time, eight months into the study (p. 76), the pilot tests of the examinations will also be beginning, and OTA will be able to review the contents of the questionnaire and examination as well as the participation rates in the interview (questionnaire) phase at the same time.

OTA suggests that CDC provide specific information about methods to be used by interviewers and about methods to "blind" interviewers about which cohort the veteran is in. It is recognized that blinding throughout some interviews is impossible. For instance, a veteran in the non-Vietnam service cohort of the Vietnam experience study will have to disclose that fact to the interviewer. Nevertheless, efforts can be made to structure the interview so that such disclosures come near the end.

Birth Defects

The degree to which birth defects will be addressed in these studies is not clear from the protocols. CDC expects to learn a great deal about birth defects in children of Vietnam veterans from its ongoing study, including a measure of association with Agent Orange exposure. Several OTA Advisory Panel members expressed concern that, even given the information that will be available from the birth defects case-control study, more attention might be paid to the subject in these studies. Birth defects are of major concern to veterans. OTA suggests that additional consideration be given to birth defects in CDC's development of the interview questionnaire.

An important factor in collecting as much information as possible is that the reproductively-active years for Vietnam veterans is passing. The probability of

collecting valid information decreases with the passage of time.

Chromosome Studies

OTA suggests that CDC reconsider its position that it will not carry out chromosome analyses. CDC's reason for not doing so, that no medical conditions are associated with chromosomal aberrations is correct. However, if chromosomal analyses for gaps, breaks, and other abnormalities were done on, say, 500 of each cohort in the Agent Orange study and no differences were found, it would answer questions about whether or not there were any such effects. On the other hand, if elevated frequencies of abnormal chromosomes were found, it might be possible to related the elevated frequencies to other effects in the cohorts. These analyses cannot be carried out on stored blood samples; they would have to be begun within a day of drawing blood from the veteran.

Liver Function Studies

CDC might also consider doing more sophisticated biochemical examinations on some proportion of veterans. For instance, liver disease has been suggested as being related to Agent Orange exposure. A thorough biochemical analysis of liver enzyme function on some veterans seems advisable to supplement the screening tests for liver function to be carried out on all veterans.

Psychologic and Neuropsychologic Testing

The battery of proposed psychologic and neuropsychologic tests has strengths and weaknesses. The Minnesota Multiphasic Personality Interview, the Halstead-Reitan Neuropsychologic Tests, and the Wechsler Memory Scale are all well-validated tests, which will provide reliable information for various psychologic and neuropsychologic parameters. The value of the Armed Forces Qualification Test is

unknown. There is evidence that it was not administered in a standardized manner at the time of induction into the service, and interpreting results of the retest will be difficult. Nonetheless, it may provide some valuable information.

Validation studies of the Diagnostic Interview Schedule (DIS) has recently been completed. Thus far, standardization has been less successful than hoped for; a great deal of inter-rater variability has been reported. The Psychiatric Epidemiology Research Interview (PERI) is still being developed, and may be a modification of the DIS, designed to relieve some of the problems identified in the validation studies. Final decisions about using the DIS and PERI should await further validation.

Possible substitutes for the DIS and PERI are the General Health Questionnaire (GHQ) and the Present Status Examination (PSE). The GHQ can be used as an initial screen. Those scoring high could be given the more in-depth examination. Both of these tests have been used for many years and are well-validated. The PSE is particularly good for schizophrenia, anxiety, and depression.

Another possible addition to the battery is the Social Functioning Examination (SFE). This examination provides an assessment of interpersonal relationships, including employment and family. It is reliable and well-validated. This might be an appropriate instrument for the Vietnam Experience study.

CDC states that it plans to consult with experts in the field in designing the psychologic aspects of the questionnaire and the psychologic and neuropsychologic examinations. The population studies group within the epidemiology group at the National Institute of Mental Health is suggested as consultants or collaborators in designing the questionnaire and examination.

Selection of Individuals for the Medical Examination

CDC proposes to examine 2,000 men from each of the five 6,000-man cohorts of the Agent Orange and Vietnam Experience studies. In their Jaunary 1983 outline and in the protocols they state that the 2,000 will be random samples from each cohort. In its review of the outline, OTA suggested tht CDC consider somehow targeting a portion of the 2,000 to "enrich" the sample and improve the chances of detecting significant medical conditions.

Although there remains some sentiment among some OTA advisory panel members that enrichment is advisable, the more general consensus is that not enough is known to do it. Furthermore, enriching for any reason in studies that seek to compare outcomes between different cohorts would introduce sampling and analytical problems.

Data Analysis and Quality Control

A major issue in data analysis is timing. The protocol designers have obviously struggled with the best approach to analysis and release of data. They would like to make the fullest use of data as they are amassed, to reorient the study if necessary, and to identify any strong associations as quickly as possible. CDC recognizes the dangers of basing conclusions on early results. They plan to release data only at the completion of study phases, and not at the the time that interim analyses are done. Furthermore, CDC intends to publish its results in peer-reviewed journals, which will provide a further check on the accuracy of its analyses. The only exception to the policy of delaying release of results until the study is complete would be finding a health effect of such importance that delaying release of the information would be unethical. Decisions to release data in such a case would be made by CDC in consultation with the study steering committee.

OTA finds this plan for release of data to be entirely appropriate, but recognizes that there may be pressure to release preliminary data. CDC might consider establishing some mechanism to protect against this pressure.

FOI injunction possible ?

cluster analysis

CDC have not yet indicated how they intend to use the vast quantity of medical data they will be collecting from interviews and from medical examinations. Numerous characteristics will be measured, many of which have no known connection with specific diseases, or more specifically with diseases in any way througt to be associated with Agent Orange or service in Vietnam. It is important for CDC to consider how these pieces will fit together to identify Agent Orange or Vietnam experience syndromes, and how they will decide what will be considered significant. This is an undoubtedly difficult and perplexing aspect of the study, but also the most critical.

CDC recognizes the need for quality control in all aspects of the study, from the conduct of interviews, the review of records, to the analysis of samples in laboratories. Specific procedures have not been laid out in any detail, but there is a sound basis for believing that appropriate measures, such as reinterview of a fraction of veterans, will be taken. OTA may have further comments when more details on quality control are presented as we move into the phase of monitoring the conduct of the study.

CASE-CONTROL STUDY TO DETERMINE THE RISKS FOR
SOFT-TISSUE SARCOMAS AND LYMPHOMAS AMONG VIETNAM VETERANS
(SOFT TISSUE SARCOMA/LYMPHOMA CASE-CONTROL STUDY)

Description of the Study

In this study a group of men with soft-tissue sarcomas and lymphomas will be compared to a group of men similar in age and race, who do not have either of those cancers. The proportion of each group that served in Vietnam and/or was exposed to herbicides in Vietnam will then be compared. A higher proportion of exposed Vietnam veterans in the cases than in the controls would indicate an association between Vietnam service and exposure to herbicides in Vietnam and subsequent appearance of sarcoma or lymphoma.

Cases and controls will be between 30 and 49 years of age during the years when data will be collected. That age span includes most all Vietnam veterans. Cases will be identified through the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, a system which seeks to ascertain all newly diagnosed cancers (cancer incidence) in 10 areas around the country that represent about 10 percent of the U.S. population. SEER centers have been used successfully for other large case-control studies during their approximately 10 years of operation. Controls will be drawn from the same population base covered by the SEER centers, using "random digit dialing," a method of population sampling based on telephone numbers.

The study will collect data over a 4 year period and include all cases diagnosed between July 1984 and July 1988. The aspect of the study which demands such a long period is the desire to accrue sufficient cases of soft tissue sarcoma for the study to be powerful enough to detect a 2-fold increase in incidence. CDC

has estimated that there will be about 900 lymphoma and 160 soft tissue sarcoma cases by the end of four years. They intend to include 1800 controls. All interviewing of both cases and controlswill be conducted by telephone.

An estimation of each case's and control's exposure to Agent Orange will be made by the Army Agent Orange Task Force, using the same technique being used to determine exposure status for Vietnam veterans included in the ongoing birth defects study.

Power of the Study

OTA is concerned that CDC may have overestimated the power of the soft tissue sarcoma/lymphoma study to detect an association with Vietnam service and/or exposure to herbicides in Vietnam. The possible overestimate stems largely from an overestimate of the prevalence of Vietnam service among individuals in the age group which will serve as controls for the study.

Power calculations in the protocol are based on an expected 10-15 percent prevalence of Vietnam veterans in the SEER-area populations. OTA compared the age structure of the 30-49 year-old Vietnam veteran population with the age structure of the SEER populations in the same age range (see Appendix A). Adjusting for differences in the age structures, OTA estimated the prevalence of Vietnam veterans to be about 8 percent. That figure does not consider other factors that might reduce the prevalence of Vietnam veterans, particularly the question of whether veterans are underrepresented in SEER areas. There is obvious value in having a reliable estimate of the prevalence of Vietnam service in the population before beginning a four-year study, such as the one proposed by CDC. A survey in some or all SEER areas to determine the prevalence could be incorporated into the pretest of this study. Without that determination there appears to be a risk of starting the study and finding out after a year or two that the study lacks the expected power.

The study may still have sufficient power to detect increases larger than 2-fold. It might be more realistic to base the study on the expectation that a 4- or 5-fold increase, would be detected particularly since the studies that detected increases resulted in estimates of relative risk of about 5 to 7.

If CDC determines that it is critical to detect a relative risk of 2, they may need to increase the number of cases collected by adding other registries. As CDC is aware, a new SEER registry is being added. Proposals have already been submitted, with an initial review scheduled for mid-July. It is possible that the new registry will be in place by the time this study begins. The cases from the new center would boost the power of the study.

The effect of a lower prevalence of veterans will be less serious for the lymphoma study, because lymphomas are not so rare as soft tissue sarcomas. However, power calculations for that study require reassessment.

Focus of the Study

A second major concern about the study is its focus. The foundation for the soft tissue sarcoma/lymphoma study is carefully laid in the protocol. There is general agreement that the scientific basis for studying these neoplasms is stronger than for any other specific health effect at this time. The hypothesis is based on several studies demonstrating an increased risk of sarcomas and lymphomas after exposure to phenoxy herbicides in occupationally exposed populations. There is, as yet, no indications that Vietnam veterans as a population are experiencing higher incidence rates of these cancers, nor would that be expected based on the hypothesis.

OTA is concerned that the emphasis of the study should be more clearly on exposure to herbicides in Vietnam rather than on service in Vietnam itself. If there is an association with exposure to herbicides, the ability to detect it would

be weakened by considering all Vietnam veterans as exposed. If it is thought that all Vietnam veterans had significant exposure to herbicides, it would not be possible to do the Agent Orange study, in which it is assumed that some significant percentage were likely not exposed.

At present there appears to be no way of estimating the proportion of Vietnam veterans who will be classified as "likely exposed" to Agent Orange for this study. However, the Army Agent Orange Task Force in using the same system to be used in the case-control study for classifying veterans included in the ongoing birth defects study, and information bearing on that question might be available soon.

In rethinking the power of the study, CDC might consider the power to detect an association with exposure to herbicides in Vietnam at several prevalence levels, and for relative risks about 2.

Control Groups

Some OTA Advisory Panel members suggested that consideration be given to including a second control group. This would most likely consist of other diseased individuals, either individuals with other forms of cancer or with diseases unrelated to cancer. Including two different types of controls is not uncommon in case-control studies, and it could enhance the scientific validity of this study. OTA suggests that CDC consider such an addition.

Timing of the Study

The length of the study as planned is dictated by the time required to collect soft tissue sarcoma cases. Lymphoma cases will accrue at a rate several times that of sarcomas. It appears possible, therefore, that results for the lymphoma study could be available earlier than results for sarcoma.

Classification of Cancers to be Included in the Study

Soft tissue sarcomas and lymphomas include a number of distinct tumor types. It is not clear from the protocol what the definition of each of these will be for the purpose of the study. This point deserves clarification.

OTA MONITORING OF THE STUDY

Public Law 96-151 mandates that a protocol for the study be developed that satisfies OTA requirements for approval and that OTA monitor the conduct of the study. OTA approves the draft CDC protocols as they stand, but there is no clear demarcation between approving the protocol and monitoring the study because certain aspects of the protocol are going to be developed as the studies progress. For instance, the questionnaire will be developed through consultation and pretest and pilot studies that will not be completed until the eighth month of the study.

Given the admixture of protocol design and development along with execution of the study, OTA proposes that it continue to participate in the study on a flexible schedule. It is appropriate that OTA review the progress in the study at the eighth month when the questionnaire will be complete and the medical examination ready for pilot testing. At that time, OTA can decide the next appropriate milestone that warrants its undertaking a review of the study's progress.

In any case, OTA plans to hold meetings of the Agent Orange Study Advisory Panel at intervals no greater than one year. Meetings will be held more frequently as important milestones are attained, but they will not be scheduled to satisfy a desire to hold more frequent meetings. The membership of the Advisory Panel may be expanded or changed as OTA's activities turn more to monitoring the study's execution and away from approving the study plan.

The participation of the Advisory Panel in the OTA review function has been essential. The members have brought information, knowledge, and insights of great value to the review.

Between the times of OTA's formal reviews of the studies, OTA staff will keep abreast of CDC's activites and make periodic reports to Congressional Committees.

APPENDIX A

Estimation of the Prevalence of Vietnam Veterans in SEER Populations

OTA estimated the prevalence of Vietnam service that would be expected in males ages 30-49 in the SEER population for the year 1986, the third year of the proposed four year study. Prevalence will differ somewhat from year to year, as men pass through different age classes, but the variation should not be great.

There is not enough information readily available to allow great precision in OTA's calculations, and the calculations given here are not meant to be exact. The 1986 population figures are derived from several sources. The total U.S. male population figures come from 1980 census data projections to 1981; figures for 1986 were taken from each preceding 5-year age class, e.g., the 1986 figure for 30-34 year olds is the 1981 figure for 25-29 year olds. Obviously, some of those people will have died before 1986, but since death rates are relatively low in the young ages included in this study, the effect should not be great. Figures for the number of Vietnam era veterans come from the Veterans Administration's Data on Vietnam Veterans (VA, 1981). Figures for the SEER male population come from 1976 figures (National Cancer Institute Monograph 57) projected forward 10 years (e.g., the figure for 30-34 year olds in 1986 is the figure for 20-24 year olds in 1976).

Based on these calculations, 8.3 percent of the general male population age 30-49 in 1986 will be Vietnam veterans. The age distribution of the SEER male population is similar to that of the general male population, thus the expected prevalence of Vietnam service in the controls is also about 8.3 percent.

ESTIMATED PERCENTAGE OF VIETNAM VETERANS IN SEER CONTROL POPULATION PROJECTED TO 1986
FOR THE SOFT TISSUE SARCOMA/LYMPHOMA CASE CONTROL STUDY

	1	2	3	4	5
AGE	U.S. Male Pop.[1] ($X 10^3$) Number (% distribution)	Vietnam Era Vets[2] ($X 10^3$)	Vietnam Vets[3] ($X 10^3$)	% Vietnam Vets in U.S. Male Pop.[4]	SEER Male Pop.[5] Number (% distribution)
30-34	9995 (31.0)	1528	492	4.9	980 (30.5)
35-39	9273 (28.8)	3375	1087	11.7	907 (28.2)
40-44	7087 (22.0)	2755	887	12.5	740 (23.0)
45-49	5896 (18.3)	583	188	3.7	590 (18.3)
	32,251 (100)	8241	2653	8.3*	3217 (100)

Percentage Vietnam era veterans in U.S. male population ages 30-49: $\frac{2653}{32,251}$ = .083 X 100 = 8.3%.

[1] Projected from 1981 population estimates (U.S. Department of Commerce, Bureau of the Census, Statistical Abstract of the United States: 1982-83 (103d edition) Washington, D.C., 1982).

[2] Projected from 1981 estimates (Veterans Administration, Data on Vietnam Era Veterans, Washington, D.C., September 1981).

[3] Derived from Veterans Administration estimates of 2926 X 10^3 Vietnam veterans in civil life as of 1981; and 9087 X 10^3 Vietnam era veterans. Assuming a constant ratio for each age group, 2926/9087 = .322 Vietnam veterans as a proportion of all Vietnam era veterans. Col. 3 = Col. 2 X .322.

[4] Col. 3/Col. 1

[5] 1976 data projected forward 10 years (National Cancer Institute, Cancer Incidence and Mortality, 1973-77, NCI Monograph No. 57, June 1981).

APPENDIX B

Written Comments of OTA Advisory Panel Members

The following comments were received by OTA from Advisory Panel members.

Review #1

The protocols described in the draft submitted by the CDC overall are well conceived. The document clearly is the effort of a professional group of individuals who are familiar with the opportunities and limitations which characterize epidemiologic studies of the nature required by this program.

This reviewer is particularly impressed with the recent and relevant experience that the CDC group has had in the Cancer and Steroid Hormone Study and the currently pursued Birth Defects Study. Many of the techniques which are already in place from these experiences should prove useful in the conduct of the various studies described in the protocols under review. The overall competence of this group is also clearly illustrated by the excellent "groundwork" which has been done in the preparation of these protocols. For example, a visit to the St. Louis National Personnel Records Center by CDC staff has provided a good sense of the individualizing characteristics of army veterans who served during the period 1966-1971. They also have initiated a locater study and soon should have some good appreciation of IRS assisted location of study subjects. The interactions with the SEER in assessing the level of cooperation that can be anticipated in the lymphoma/sarcoma study also gives this reviewer a sense of confidence that these workers will pursue their tasks in a disciplined and vigorous manner.

An important feature of the draft document is the various efforts to "stage" and pretest the more important procedures which are to be followed. It is clear that these workers intend to take as much advantage as possible of the early information gained in their efforts to improve the quality of the various studies. One must admit that at this stage of the gaime it is difficult to identify in any detail the precise manner in which these ongoing revisions will be approached. Nevertheless, there is little doubt that procedural weaknesses will be encountered and that conscientious restructuring of some aspects of the protocols will be likely to be beneficial to the overall program.

A careful reading of the document has convinced this reviewer that the authors are well aware of the many limitations and compounding elements which necessarily are associated with a study of this nature. The following issues are raised as points for discussion by the review panel:

1. The Viet Nam Experience Study—It is this reviewer's opinion that it is unlikely that well defined information will emerge from this effort. In general, it may be reasonable to anticipate that the experiences of a typical draftee serving in a hostile environment are likely to be "hazardous to one's health." Considering the enormous complexity of the Viet Nam experience, the possibility of identifying long term specific health outcomes related to these experiences are probably fairly remote. The most likely area to give rise to as yet unidentified health parameters might be in the psych-social arena. Almost by definition these health outcomes are likely to be vague and difficult to relate specifically to "soldering responsibilities."

2. Encounter Scoring—Clearly one of the most tenuous aspects of this epidemiological study will involve the scoring of individuals with respect to "likely exposure" versus "unlikely exposure." The authors are well aware of

this difficulty. In an effort to minimize the ambiguities arising from the assignments of unit encounters, the authors propose to use three tabulating systems. It is noted that these systems are arbitrary and therefore the justification for the scoring systems presented is unclear.

3. Health Outcomes--A second major difficulty with the study is the vagueness of the health outcomes which are to be identified. In view of the breadth of the examinations to be given to the participants in these programs, one can only hope that early identification of probable outcomes associated with exposure to Agent Orange will be made during pretests and/or pilot studies. Based on the nature of the discussion one can assume that barring major disappointments during the early phases of these studies, the CDC staff will pursue its full committment to the entire study. Perhaps it would be useful to establish as soon as possible some decision points (go/no go decisions) concerning specific goals.

4. Participation--CDC recognizes the problems which may be associated with the level of participation in the examination phases of study. Their comment concerning "VIP" treatment of the study subjects is certainly valid.

5. Additional Points--Some relatively minor points that may be worth considering include the following:

a. The workers should insure that they stick with the principal goals of the studies. Thus, it may not be particularly relevant to determine if there is any relationship between voluntareerism and health (page 22) or to extend the question of the "Viet Nam Experience" to the "Korean Experience" and "European Experience" (page 32).

b. The authors hope to be able to determine if medical tests are relevant during the early phases of this study. Procedures by which these determinations are to be made are vague.

c. How will the examiners be kept blind with respect to which cohort a particular individual belongs (page 47)?

d. It would be useful to have information on the credentials of the staff who will be responsible for carrying out these studies.

Overall, as mentioned at the outset, this is a first rate document which has been prepared by well informed individuals in a careful and systematic way. It seems reasonable to expect that the successful execution of this study will provide useful answers to many of the outstanding questions of the possible long term health consequences of the exposure of the Viet Nam veterans to Agent Orange.

Review #2

Critique

The principal limitations of the study are described in the protocol.

Of first priority among limitations is the absence of a prior hypothesis of sufficient strength to make an effort of this magnitude defensible as a scientific investigation. It is then accepted that the investigation is to e undertaken for other than scienfitic reasons, and further critique relates to the adequacy of the study plan to accomplish this non-specific purpose.

In these terms the study is probably feasible at very great expense. It remains to be determined how successful the investigators may be in locating the 18,000 subjects and in obtaining the 6,000 special study subjects. It is reasonable, however, to believe that adequate participation is possible. Even in absence of this phase of the study, mortality study through the National Death Index from 1979 to an unsepecified future time seems clearly feasible.

Furthermore, it may be assumed that a very large proportion of the study cohort is alive as of 1979 (identified as active enlisted military men in 1967-8).

Specific Items of Critique

1. Sample size and power

The investigators correctly study power relative to doubling effects (relative risks of 2) or greater. In an observational study (without intervention by the investigators) it is rarely if ever possible to make useful interpretation of findings of smaller effects. These cannot be distinguished from possible or probable effects of recognized or uncontrolled confounding or misclassification. With suffciently large effects it is generally felt reasonable to infer that unrecognized confounding and misclassification is unlikely to account for the result.

2. Intervention instrument

One might hope that the investigators would have progressed further with development of the interview instrument. A principal unfavorable criticism in the review of the prior draft was lack of development of the means of morbidity assessment. Specifically the plan was criticized as being too shallow in morbidity areas where specific hypotheses might be proposed. The present protocol comments on this issue, but the specific means of assessment is to be developed.

3. Breadth of assessment

The protocol is correct in including a broad morbidity and total mortality assessment. This is necessitated by the assignment to the

investigators, relating to the wide range of adverse outcomes summarized in Table 4 as potentially related to Agent Organge.

4. Limitation of influence

The section on study limitation, is correct in noting that definitive conclusions cannot be anticipated. This again relates to the assignment. Rare outcomes, such as specific malignancies, cannot be expected to be demonstrated to be affected, and this is in part the stimulus to the new study, of lymphoma and sarcoma. More severe are limitations, described by the investigators, of interpretation of positive findings that may be expected to arise in such a broadly directed study. The investigators describe methods for assessing such results. I believe their plan is appropriate and in agreement with the best information available for such analysis and interpretation.

5. Association of late outcomes with chloracure and other acute outcomes

A different approach to exposure might involve defining a special exposure category as subjects with acute effects ascertained in interview, if not other soucre of information is found. It is possible to plan this as a phase of analysis of the present study.

Review #3

I have reviewed the Agent Orange Vietnam Experience Study from the Center for Disease Control. The protocol is much better than those previously submitted, especially the addition of the case-control study. There, however, remains several major weaknesses.

1) The sample to be examined, approximately 2,000, should be stratified based on the results of the initial interview. This stratification would be based on the answers to specific questions suggesting any illnesses that might be related to Vietnam or agent organge experience. A random sample would then be selected of those individuals who had low risk. By using a stratified sample, the power of the examination of 2,000 will be substantially increased.

2) The interview and examination proposal remain extremely weak and suggest little chance of any great success unless there is a very obvious association with a disease or group of disease and either Vietnam experience or exposure to agent orange. Rather the methodology of doing both the interview and examination have a very high probability of resulting in a spurious association. The psychological questions proposed are inadequate and need to be carefully reviewed. It appeared that behavioral change or psychiatric abnormalities may be a most important outcome. I therefore would suggest that the population studies group, that is within the epidemiology group at the National Institute of Mental Health, take a careful look at this quenstionnaire and in fact it may be advisable for them to take on the responsibility of designing the behavioral questionnaires in collaboration with the Center for Disease Control.

3) The physical examination proposal is also poorly defined. The CDC apparently believes that utilizing the format of the National Health Examination Survey would be worthwhile. To me this makes very little sense. The National Health Examination Survey aims to measure the prevalence of biological variables and relatively common diseases in a defined population in the United States. The CDC examination on the other hand, should be aimed to test for detailed specific hypthesis .... The measurements of the urine, blood, liver especially are completely inadequate. My recommendation again, is to have the physical examination and especially the laboratory measurements carefully reviewed by experts in each of the fields prior to utilizing the examination format. The laboratory measurements will probably be far more important than the actually phisical examination and objective laboratory measurements should be carefully evaluated prior to beginning the physical examination phase.

4) The selection of cases, i.e., prospective cases for the case-control study is certainly scientifically valid but will not result in any useful data perhaps until 1988 or later. By this time I would suspect that numerous case-control studies will have been completed and that the information from the CDC study may be additive even perhaps superfluous. I think it is feasible to use both prior cases, as well as current and subsequent cases and to expand the study to include both the

areas that are presently proposed but also the large number of hospital registries and state cancer registries. By increasing the number of cases in this matter, it should be possible to complete this study within a few years.

5) The selection of controls for the case-control study also has some particular problems. The CDC study proposes to use only a living control. I believe that a disease control, that is someone with another disease should also be considered. This will make the study a little more difficult to do but will substantially enhance its scietific merit. It is possible for example, that the relationship between sarcoma-lymphoma and Vietnam or agent orange experience is a function of the selection of the kinds of individuals who went to Vietnam or were exposed to agent orange and that such individuals either prior or subsequently or were more likely to be exposed to the specific agent that resulted to sarcoma or lymphoma, or for that matter that their health behaviors are such that there is an increased frequency of many different diseases. One way of dealing with this problem would be to include a disease control, as well as a living control. A simpler disease control might be individuals with another cancer other than lymphoma or sarcoma or some other chronic disease which is commonly associated with hospitalization and relatively easy to diagnose.

Review #4

We were very much impressed with the Protocol upon reading the first draft. As we studied it in depth, we were pleased to note that the investigators had anticipated the many problems and concerns we felt to be inherent with this type of study. Our overall impression is that the Protocol was well thought out, and with few exceptions is outstanding.

We have three recommendations to inject to the committee based on our review of the Prtocol:

Section 4.2.
In regard to location of study subjects, we feel that the VFW and other service organizations' membership rolls may be of tremendous assistance in providing current addresses of those chosen by CDC to participate in the cohorts that are not identifiable by IRS or Social Security. Therefore, we recommend that a dialogue be

established with the service organizations to cooperate in this effort without jeopardizing the cohort selection process. We are exploring this possibility within the VFW without violating the privacy of our members.

Section 4.3.1.2.2.
We realize that the standardization of testing is extremely important to the epidemiologic studies. Ideally, one test site would be best; however, we recommend that a minimum of four sites be selected which could be located in transportation hub cities such as New York, Atlanta, Dallas, and San Francisco. CDC would still be able to maintain their standardization and the participants would find transportation easier.

Section 4.5.1.2.
There may be some participants who will experience difficulty with employers regarding time to take part in the studies. In the event that repercussions develop, consideration should be given to the protection of employment rights under Chapter 43 of Title 38. The Department of Labor's Solicitor General's opinion should be sought to determine if this can be considered a military related activity for the purpose of protection under this chapter. It is felt that this would enhance participation by those individuals selected.

Review #5

The manner in which the Centers for Disease Control has progressed since accepting the responsibility for the Agent Orange study is encouraging. In addition, is felt that the Vietnam Experience study and the case-control studies of the incidence of soft-tissue sarcomas and lymphomas, are of extreme importance.

Although I do not question the CDC proposal to limit the Agent Orange study to draftees and single item enlistees in the enlisted ranks of the Army, it should be expected that there will be criticism from some veterans of other branches of service, and those categories of Army service that are not included.

There is a great deal of concern expressed in the draft regarding the possible difficulty in achieving a high rate of participation among those

individuals chosen for the studies. As previously offered, the American Legion will encourage such participation by Vietnam veterans through every means available to disseminate information.

On page 79 of the draft it is stated that CDC will conduct the studies with guidance from a steering committee, and it has been requested that a subcommittee of the panel which provides oversight of the Ranch Hand studies be formed for this purpose.

It is understood that this committee consists of medical and scientific experts from the private sector, and is chaired by Dr. Jack Moore. The inclusion of a representative of the Vietnam veteran community on the committee could well prove to be beneficial, both for the availability of knowledge on conditions that existed in Vietnam, and to assure concerned Vietnam veterans that their interests in the studies are being represented on the steering committee.

It appears that no decision has been made as to who will conduct the examinations, and where they will be performed. As you are aware, this will be an important factor with respect to the participation in the studies by the selected veterans.

Some concern has been raised by a member of the OTA Advisory Panel as to whether the studies should be carried out because of the pending legislation in Congress relating to the presumption of service connection for certain disabilities based upon Agent Orange exposure. I strongly feel that these legislative measures should in no way affect the CDC studies, and that the research should proceed as planned.

Review #6

A great deal of effort has been expended in these protocols to ensure that an effect, if due to dioxin, will be detected. They will look for effects which have been identified by animal studies as well as by a variety of human studies and they acknowledge that there is still the real possibility they will have false positives, false negatives, and also equivocal findings despite this effort. I like the stated recognition that these protocols will be able to handle the biases if they later change protocols. If they change protocols, biases will be difficult to control.

In any of their three cohort studies, including "likely exposed" may identify a cohort with more combat duty, and with this selection there may be increased deaths, increased casualties, or even increased drug usage. This possibility is not considered in the protocol - maybe they can identify this possibility by comparison to the "likely not exposed," or even to cohort 3. World War I had its "gassed syndrome," World War II had its battle fatigue and tropical diseases, and Vietnam had its drugs and other known confounding factors.

I believe that the definition of cohorts in St. Louis should prevent biases, but the examinations of the veterans can be biased by the questioners, by the physical examiners, or even by those who decide they want to take the exams. From what I know of Ranch Hand, I believe that these possible biases have been well handled.

I now would like to list some of my specific comments for the various pages of this protocol.

Page 8, first paragraph. It states that it is possible that a significant exposure was from non-Ranch Hand applications. They do not give the basis for this statement and it would seem that this could not be a major source of exposure.

Page 9, second paragraph. It states that for the occupational exposure, the total number of exposed persons was usually not reported, but, in fact, this exposure list is recorded in a number of books and summaries. I believe this paragraph should also address the fact that 2,4,5-T was used widely and indiscriminately over a number of years in the United States and without reported effect over these many years.

Page 10, first paragraph. This paragraph talks about liver effects, but it does not acknowledge or recognize that these liver effects were temporary in practically all reported cases.

Page 11, the last paragraph. The statement is made that literature suggests that Vietnam veterans differ from other veterans in a number of ways. This protocal does not state how they will deal with these many confounding factors.

Page 12, second paragraph. It states that the servicemen enjoyed better long-term health than their counterparts who did not serve in the military. I suspect that they are dealing with the so-called healthy worker effect. Nevertheless, a comparison between the military and non-military would be an interesting definition of long-term health status.

Page 12, last paragraph. The first sentence states that there are no studies comparing the health of combat veterans with those who did not participate in combat. I would think that the reason there are not reports is that those in combat did not suffer effects other than those who were not in combat. This would account for why there are no reports.

Page 17, ninth line from the bottom. It states that if differences existed and they applied to all veterans, then a valid study of Vietnam experience would not be possible. I don't see how they reach such a conclusion; if there is no difference seen, then there is not a Vietnam effect.

Page 18, second paragraph, fifth line. They are discussing the Swedish finding of soft tissue sarcomas but they fail to address the negative studies done similarly to the Swedish studies which found no effect. These studies include the Finnish and the New Zealand studies. See attached analysis.

Page 18, fourth from the last line on second paragraph. They state that other cancers could be added easily if an association was suggested. Based on a form of this lymphoma study, I don't see how the other cancers could be identified

Page 35, first paragraph. This paragraph implies that the Swedish study has established an effect between the exposure and sarcomas. I have no problem with them attempting to prove Hardell's conclusions, but I do not believe that Hardell's conclusions are fact. I see no reason for not including cases

which arose prior to 1984 as a part of the soft tissue sarcoma study. Again, see same attached analysis.

Page 44, first paragraph. This paragraph states that mroe emphasis will be given to dermatologic and immunologic studies for the Agent Organe cohort and for psychologic outcomes for the Vietnam cohort. Such an approach would encourage bias. The interviewer should not know which group an individual is in. A standard protocol should be used which would be constant, regardless of the response of the individual.

Page 44, second paragraph. It states that all the factors may be associated with service in Vietnam. They are indeed correct and these same confounders will be found not only in the non-service cohort but also in the Agent Orange cohort as well.

Page 44, third paragraph, fourth line from bottom. Though the subject's perceptions about exposure to herbicides are indeed appropriate, the same question should be addressed to the "exposure unlikely cohort" as well as the third cohort. After receiving replies to these questions, the remainder of the questionnaire should be followed just as though there had been no discussion of exposure to herbicides. Only in this way will biases be prevented.

Page 46, paragraphs one and two. There is no question but that servicemen with complaints will be more likely to participate in the study than a man without complaints. This will create a bias. This section does deal with the importance of well-standardized, non-biased approaches and it certainly is well stated.

Page 71, first paragraph. Though it states that this high risk is generally suspected to be exposure to Agent Orange, one of the reasons CDC has been asked to do the study is that many experts do not think that exposure to Agent Orange produces risk. Nevertheless, it is the possibility of high risk that is the basis for this study by the CDC. As stated earlier in the protocol, there are many other factors which are, not may have been, factors which can confer as increased risk. The last sentence in this paragraph acknowledges that being in Vietnam poses health risks which should be identified.

Review #7

Generally, I find the protocols clear, straightforward, well thought out, logical and orderly in their development. The research plan is nicely detailed and meticulously developed. There is little with which I can disagree in this proposal (although, there are some specific questions and reservations I have in my detailed comments that follow). In my view, the investigators deserve high marks for this effort and I would heartily endorse their embarking on the specified work.

One general comment I have concerns the degree of coordination with the VA Twin Study that is about to commence. Although I see merit in independence of the two studies, both studies have common methodologic issues and usage of some of the same record sources. I would hope that there would be sufficient coordination between the two studies so that duplication of effort can be avoided and that "discovered wheels" in one study can be deployed rapidly in the other to enhance progress.

p14, L4-5 foot. I find this statement of uncertainty of exposure a most important point. I'm glad the investigators made this point and, to me, it's a reflection of the care and thought they have taken in developing this protocol.

p16, L4-6. Perhaps I'm missing some important concept here, but I do not see clearly just what are the "problems in analysis and interpretation" entitled by the lack of a fourth cohort constituting herbicide exposure and "Service Experience B." I take no issue with the proposed three cohort design. I would very much appreciate some elucidation of precisely what has been compromised by exclusion of this fourth cohort.

p20. Is it possible for subjects to be in <u>both</u> studies?

p24 bottom to p25 top. I hope that a record will be kept of the number of battalions excluded from the study because they exceeded the number of permissable gaps.

p29, L13-15. Here, too I hope a record will be kept of those individuals deemed ineligible.

p31, bottom. The methodology described here sounds similar to that proposed for the VA Twins Study. (Note that two members of the OTA Panel also serve on an advisory panel to the VA Twins Study.) Will there be any attempt to coordinate the efforts of these two studies and avoid unnecessary duplication? Both the CDC study and VA study will rely to some degree on review of the St. Louis records.

p33, L3 foot. I don't believe the SEER program people at NCI would like this statement. I suggest deletion of "nearly all"; SEER's intent is <u>complete</u> registration of all incident cancer in the area (save for non-melanoma skin cancer and a few other exceptions).

p34, top. The CDC investigators should be aware that SEER is expanding. There has been an RFP for a new SEER Registry. Initial review of the submitted proposal will occur in mid-July. It is possible that the new SEER Registry may be announced or even in place by the time this study begins.

p40, L11-12. The suggestion of capture-recapture methods to estimate underacertainment of deaths sounds intriguing. Can the investigators provide a reference describing these techniques for this particular purpose?

pp40-41. It's not quite clear to me what the investigators will do if the hospital records provide information different from that on the death certificate. Will they then change and recode the causes of death on the certificates?

p45, L3-5 foot. I agree that it's a good idea to delay specification of the sampling design for selecting examination candidates until at least the pretesting has been completed.

p52, middle para. I find this a most important point which is well stated. I agree that some firm idea of the magnitude of prevalence is indeed essential for meaningful power considerations and that information of this nature simply isn't available now on the target populations for this study.

p52, L4 foot to p53, L3. One might point out, however, that the power will not be particularly good for individual cancers - even the most common ones. If exposure increases cancer risk, what is the more biologically plausible hypothesis, that it produces an across the boards increase for all cancers or that it acts by increasing risks of particular cancer sites? If the latter, alas, the study will not have much power to detect this.

p53, bottom paragraph. I find this, too, a thoughtful and indeed pertinent discussion.

p55, last paragraph. I agree wholeheartedly with the notion of comparing the participants and non-participants.

p63, L2-4 foot. I have some reservations about the wisdom of analysis on a regular basis as the data are accumulated. This poses problems in interpretation of resulting p-values. Are the investigators proposing a formal sequential analysis plan? The project already entails the statistical problem of multiple comparisons with the lack of specific hypotheses regarding effects and the necessity to examine many outcome variables. To compound multiple peeks at the data with multiple comparisons may just be begging for trouble.

I note that the stated intent is "...to use the results to amplify or correct the thrust of the investigation." I'm not quite certain what this means, and wish the investigators would cite some specific examples of the nature of such amplification or correction in thrust.

p65, L7. I am puzzled here by the choice of odds ratios. The previous page indicated direct estimates of disease incidence or prevalence in the cohort studies. Wouldn't the ratios of such rates consequently provide direct estimates of relative risks? What purposes would calculation of odds ratios serve in the cohort studies? My next thought was that perhaps the paragraph referred only to the case-control sarcoma/lymphoma study. But, the latter portion of the paragraph refers to analysis of data derived from the psychological tests which pertain only to the cohort. Either the hour at which I'm writing this is too late, or some clarification is needed regarding what techniques apply to what study.

p66, top. I'm not so sure follow completely the logic here. With the example of education, my view is that even if adjustment for it does not alter the odds ratio, there still may be merit in considering it in further analysis. Although its adjustment may not alter the odds ratio, it may increase the precision of the estimate and lead to a narrower confidence interval. In other words, education may not entirely fit the criteria of a confounding variable in the epidemiologic sense, but it may be a pertinent covariate in the statistical sense and an accounting of it in analysis could lead to improved precision of the estimates.

APPENDIX B

ADVISORY COMMITTEE ON SPECIAL STUDIES RELATING TO THE POSSIBLE LONG-TERM HEALTH EFFECTS OF PHENOXY HERBICIDES AND CONTAMINANTS REVIEW.

(Ranch Hand Panel)

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 27709

Memorandum

Date September 1, 1983

From Chairman, Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants

Subject Review of Protocols for Epidemiologic Studies

To John A. Svahn, Under Secretary
Chairman, Agent Orange Working Group

In response to your request, the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants has reviewed the Protocols for Epidemiologic Studies of the Health of Vietnam Veterans prepared by the Centers for Disease Control. Committee members and Expert Consultants who participated in this review were Drs. G. Comstock, R. Hoover, R. Monson, J. Moore, P. Sartwell and I. Selikoff. The review included a meeting in Washington, DC on July 19 during which the Committee discussed the protocols and had the opportunity for discussions with two CDC scientists, Drs. D. Erickson and P. Layde.

The Committee understands that Public Laws 96-151 and 97-72 requires an epidemiological study of U.S. veterans to assess effects of exposure to herbicides and dioxin, or other environmental exposures, during the Vietnam conflict. The committee therefore reviewed the conceptual and general scientific approach of the CDC Protocols to these broad objectives. While the committee does possess a working knowledge of the U.S.A.F. Ranch Hand Epidemiology study, it did not attempt to review other proposed or ongoing studies to determine if there is unwarranted overlap with the proposed CDC studies.

The committee is of the concensus opinion that the CDC protocol shows careful, diligent, competent thought and preparation. A package of 3 studies are proposed: two cohort studies, one of which is to assess the long-term effects of potential exposure to Agent Orange, and the other, "Vietnam experience"; a case control approach to evaluate soft tissue sarcoma and lymphoma.

COHORT STUDIES

- The Agent Orange cohort study involves a "likely exposed" cohort and two comparison cohorts -- one "likely not exposed" matched for area within Vietnam and combat status and the other, where Agent Orange was not sprayed but still in Vietnam. Each cohort is composed of 8400 men and each is limited to draftee and volunteer enlisted personnel who served one tour of duty in Vietnam in the years 1967-1968. The study calls for tracing the designated individuals and administering a telephone interview. The expected response to this is 72% yielding 6000 interviews within each cohort. Further efforts will include bringing approximately 2000 persons

15-982

from each cohort in for a health evaluation that is to include a physical examination, a battery of laboratory tests and a battery of psychological tests. The interview, physical examination and test batteries are designed to obtain information on exposure, potential confounding variables and a wide variety of potential outcomes including disease and disability of almost any variety and any one of a variety of laboratory abnormalities.

The cohort study for the "Vietnam experience" is very similar in conduct and instruments used. The cohort selection is different in that a random sample of discharged veterans from Vietnam conprise the "exposed" group while a sample of veterans stationed in 3 other locales during the same time period comprise the "unexposed" cohort.

- The key issue with respect to the Agent Orange study is selection of "most likely" and "likely not" exposed cohorts using the product of a records review conducted by the Army Agent Orange Task Force. The strength of the difference between the two cohorts can only be ascertained after the service record analyses are complete. It is imperative that this be clearly and prominently stated and that after the cohorts are identified, but prior to execution of the studies, an evaluation as to the specific strength and limitations of the studies be developed.

- Other comments relevant to herbicide exposure are:

  --more extensive explanation or documentation of nonaerial sources of herbicide exposure.

  --To give an idea of the sorts of things that make records unacceptable, can some comparison be made between battalions with and without acceptable records?

- Since, ..."the degree of completeness of the 'Services Herbs' data set is unknown", perhaps a pilot study of the correlation between this data source and personal recall might be in order.

- Additional thought to the weighting of exposures is mandatory. Consider weighting for recurrent exposure to the same application; clear definition as to whether the measure of exposure is the company or individual is needed; why is only one measure of proximity for non ranch hand applications required. In addition, better discussion of the cross-comparability of spray location contained in the HERBS tapes and those for company or battalion is desirable especially as it impacts on the accurary of the "one kilometer" definition of ground troop exposure.

- Several committee members felt that the ± 24,000 individuals chosen for the "Agent Orange" study could also serve as a major cohort in the "Vietnam experience" study. A comparison cohort from other duty stations, otherwise comparable to these 24,000 could be chosen and evaluated. The potential savings in manpower and money is considerable and CDC is requested to further consider this alternative.

• The committee feels that the CDC should consider a staged questionnaire approach with results of one phase leading to decisions as to the specific design of the next phase. There seems to be a desire in the current design to compress all aspects of what is a very complicated study into a concise predetermined program. It is quite difficult to get adequate cooperation to do a high quality telephone interview study of one disease where the fact of disease and its characteristics are already known. It is highly questionable if one can, as is proposed, glean facts and characteristics of all diseases particularly when the condition and co-variates of interest include some of the most difficult to measure objectively (e.g. infertility, sexual drive, depression, drug abuse, stress, alcohol use). The initial use of a screening interview followed by subsequent interviews appropriate to the results is strongly urged. Further the philosophy of this approach should impact on the protocol for the morbidity phase of the study.

• There should be firm guidelines for deciding if and when procedures are to be altered. Changes made on an ad hoc basis can lead to serious problems of potential bias and in the combining of findings before and after the changes. For example, easily found people will be interviewed and examined first. Subsequent changes will thus disproportionately affect the hard-to-find group; since the latter group undoubtedly differs in many ways from the easily found group, bias could be introduced.

• A preferred way to handle the possibility of changes is to make the decision to change after all the work has been completed on all members of a representative sample. The altered procedure can then be applied to all the larger group.

• In several places the protocol states that being sent to Vietnam was a matter of the "luck of the draw". Vietnam clearly required more combat troops than other theaters. Men without special skills were more likely to become combat troops. Careful demographic comparison will be needed to justify this assumption that chance alone determined geographic assignments.

• Issues of recall bias and its cousin, ascertainment bias are of great concern in these studies. While occasional mention is made of these issues, there is no real discussion of how they will be dealt with, prevented and assessed for each of the proposed studies.

• In the morbidity segments of the study, the standard examinations outlined in the protocol are appropriate, particularly since their service aspect is virtually an obligation to those who will be volunteering at considerable personal sacrifice for the several days of the clinical examinations. From what is already known, nevertheless, one cannot be sanguine that abnormalities which might be present as a result of Vietnam exposures and experience will be reflected in unusual results in the standard studies. It is therefore urged that consideration be given to extending the examinations to include more sophisticated studies. These might well include the range of lymphocyte/immunoglobulin studies now being utilized, for example,

in AIDS investigations; neurophysiological tests beyond nerve conduction velocity, enzyme induction, sperm studies in a stratified sample of volunteers and, despite reservations, chromosome aberrations. Also, in view of the likelihood that additional probes will be identified in the not too distant future, serum, lymphocytes and fat biopsies in volunteers might well be set aside and frozen for future tests.

• A truncated report to each veteran is planned, giving the examination results. A full report to the veteran and, if requested, to his physician should be considered. If this contains results not easily interpreted by the veteran, the suggestion that he review this with his physician could be added. In the same way, abnormalities found will not be further studied by CDC but the veteran will be advised to seek additional medical care. It will be useful to arrange for receipt of information from such further care. There is concern that anormalities will not be followed up with a more extensive work-up for a diagnosis. Isn't ascertainment of disease an integral part of the study?

CASE CONTROL STUDY

• There are definite advantages to looking at cases of sarcoma and lymphoma that developed prior to 1984. Looking at fatal cases should be sufficient. If Vietnam veterans do in fact differ in some way from other veterans related to these cancers this difference should show up prior to 1984. If Vietnam veterans do have a pre-existing increased risk the post 1984 experience would falsely attribute this to exposure. If the pre 1984 experience showed no relation to exposure while the post 1984 experience did, this would greatly strengthen the conclusion of cause and effect.

• The proposed studies currently offer little beyond other studies underway to assess these tumors. At any rate, if the CDC investigators believe they have developed a superior tool for independent exposure likelihood assessment among veterans they should seek collaboration with ongoing investigations offering this assessment as their contribution.

• For the case control study, the SEER data sets will be utilized. SEER is not totally representative of the U.S. population. It is recommended that CDC document whether or not this lack of representativeness will affect its use for this study.

• The case control study could more fully exploit the SEER data set particularly with regard to Vietnam Experience. It would add little to the investigators burden to include primary liver cancer and nasopharyngeal cancer (both uncommon tumors and both conceivably a future problem with veterans. The controls would be the same.

In summary, the committee supports the conceptual and general scientific approach contained in the CDC Protocols. It has identified several items that need further explanation or consideration. The merging of the "Agent Orange" and "Vietnam Experience" studies has some intuitive appeal and a potentially large cost savings that should be considered. A more sequenced

approach to questionnaire phases of the study and, perhaps the morbidity phase, should be incorporated into the protocol. Some Committee members felt the case control study, as designed, had a low probability of enhancing the data that should be realized through other ongoing studies. The CDC protocol should be strongly influenced by the experience learned from the current USAF Ranch Hand Questionnaire and Morbidity studies.

Finally, while the protocols represent a best effort approach to an epidemiological investigation mandated by law the AOWG should assist the CDC in restating the inevitable constraints inherent in such studies in an unambiguous way so that the issues are clearly understood by Congress, veterans, and the public.

John A. Moore

John A. Moore, D.V.M.

cc:
Acting Chair, Science Panel, Agent Orange Work Group
Advisory Committee Members

APPENDIX C

SCIENCE PANEL, AGENT ORANGE WORKING

GROUP REVIEW

August 15, 1983

Review of CDC Protocols for Epidemiological Studies of the Health of Vietnam Era Veterans

Prepared by the Science Panel, Agent Orange Working Group (Cabinet Council)

The protocols provide a careful and well-thought out plan to investigate some possible long-term health effects of exposure to Agent Orange, and other factors, among veterans who have served in Vietnam,. The protocols show an awareness of many of the problems which can be encountered in such a complex study. The formulation of three separate but related studies should make it possible to gain valuable information concerning the current health status of Vietnam veterans even if severe difficulties arise in any one of them.

CDC has proposed three studies - two of Cohort design and one Case-Control. The Cohort studies include an Agent Orange study and a Vietnam Experience study. The Case-Control study is designed to measure the association between having been possibly exposed to Agent Orange while in Vietnam and subsequent development of soft-tissue sarcoma or lymphoma.

The Agent Orange study proposes to recruit 6000 one-term selective service or enlisted Army veterans from each of three groups according to their estimated exposure to Agent Orange and combat experience while in Vietnam. Estimated exposure status will be based on existing records of herbicide applications and troop movements within the Department of Defense files and is being determined in conjunction with the Army Agent Orange Task Force. One group of combat veterans will be considered likely to have been exposed to Agent Orange because their unit was close to the recorded site of air or ground spraying of herbicides at the time of, or soon after, application on several occasions. One group of combat veterans will be considered not likely to have been exposed to Agent Orange because they were not known to have been near a herbicide application site and the third group of veterans will be selected from units serving in areas in which it is known that herbicides were not used. The third group will also not have experienced the intensity of combat of the other two groups. All of the 6000 participants from each group will be interviewed by telephone to obtain socio-demographic, military service, exposure to occupational hazards and health information. Two thousand from each group will be randomly selected and invited to particpate in an extensive medical, psychological and laboratory examination. Results of these health assessments will be compared among the three groups to determine if there is a health decrement due to possible exposure to Agent Orange while in Vietnam.

The Vietnam Experience Study proposes to recruit 6000 similar Army veterans from each of two groups according to whether or not they served in Vietnam based on personnel files at the National Personnel Records Center in St. Louis. They will be interviewed and examined in a manner similar to the Agent Orange Study. The initially selected cohorts for both of the cohort studies will be traced to determine the fact and cause of death so that mortality experience over the past 15 years can be compared as an adjunct to health assessment.

The Case-Control study will select cases of soft-tissue sarcoma and lymphoma from SEER registries across the United States. Controls will be located via random digit dialing from the same populations which are covered by the SEER registries. Cases and controls will be group matched for appropriate characteristics and will be interviewed via telephone. Interviewers will obtain information on military service, possible exposure to herbicides and their contaminants, occupational histories and other information on possible confounding factors. The proportion of cases who have served in Vietnam and/or who may have been exposed to Agent Orange will be compared to that of controls to estimate the relative risk for soft-tissue sarcoma and lymphoma among Vietnam veterans compared to persons not exposed to Agent Orange.

The following summary is based on individual reviews and discussions held in two meetings among Science Panel members and representatives from the CDC. Individual comments by members of the Science Panel are included as part of this review. The summary follows the "Outline of General Concerns" which was developed during the early part of the review process and is also included as part of this review. Recommendations regarding the proposed studies have been prepared and are attached.

SUMMARY

I. Background and Review of the Literature

The background material contained in the protocol provides a good framework for proceeding with the studies as proposed. In view of the general lack of knowledge of the specific health effects to be expected following exposure to Agent Orange, it would be helpful to include a more thorough discussion of the current complaints of Vietnam veterans which are contained in data already collected by the Veterans Administration and perhaps other veterans' organizations. In addition, some provision should be made to incorporate the findings of the Ranch Hand study as they become available.

II. Exposure Index

The development of a realistic exposure estimate for identifying exposed and unexposed study cohorts has received more attention than other issues by most reviewers. The concerns expressed have included suggestions for validation of the index and the procedures used to develop it; methods to identify cohorts with maximum differences in exposure between highly likely and unlikely exposed groups; and concerns about comfounding exposure to Agent Orange with other potentially damaging effects of Vietnam service - particularly combat experience. The Science Panel recognizes that the adequacy of any proposed procedures cannot be determined until the study is underway. The Science Panel, therefore, recommends a major reevaluation of the selection of exposed and unexposed units for potential inclusion in the Agent Orange study after these units have been tentatively identified.

III. General Study Design

The paucity of existing hypotheses of what adverse health effects might be evident 15 years after possible exposure to Agent Orange, and other factors in Vietnam makes it difficult to design an examination protocol. A general health examination would seem to provide a needed service function, but may not detect subtle health decrements evidenced only, if at all, by very specialized clinical and laboratory procedures which may not have been well standardized. Suggestions of how to remedy this include staging the interview and examinations, screening before more detailed examinations, examining a subgroup on repeated occasions, and including other more specialized examinations and laboratory tests for everyone. It is expected that some of these details will be investigated during the pilot and pretest phases of the study. The Science Panel recommends, therefore, that a reassessment of the examination and laboratory test procedures be made following completion of the pilot and pretest phases, particularly for the Agent Orange study. A thorough rationale for all procedures should be included. The results of the Ranch Hand Morbidity Analysis should also be available to assist in designing an examination schedule.

Several reviewers suggested that there needs to be a clearer delineation between the pilot study and the principal investigation. This is particularly important where decisions based on pretest and pilot phase activities will determine subsequent procedures such as the selection of cohorts, the matching of comparison groups, final determination of sample sizes, and detailed development of questionaire and examination procedures. The Science Panel suggest that major decision points be incorpoated in the protocols along with an indication of the bases on which alternative decisions will be considered.

IV. Specific Concerns

A. Sarcoma-Lymphoma Study

There has been some concern that SEER registries may not use comparable criteria for defining soft tissue sarcomas and that populations in the catchment areas of the SEER registries are not entirely representative of the U.S. The Science Panel suggests that these issues be considered in the further development of the soft tissue sarcoma-lymphoma study.

It has also been suggested that deceased cases from an earlier period, and next-of-kin interviews on these and later cases will enable the study to be completed earlier and can enhance interpretation of results. Also that other cancers, particularly liver cancer, should be included. All of these issues should be considered in the context of other on-going efforts to study the relationship between various cancers and herbicide exposure. The Science Panel recommends that CDC investigators at least get together with the principal investigators from the National Cancer Institute, the Veterans Administration and the Armed Forces Institute of Pathology to discuss the current status of ongoing efforts and need for additional studies of this subject.

B. Vietnam Experience Study

All reviewers felt that the Vietnam Experience study is appropriately designed and should provide a major contribution toward resolving Veterans' concerns of adverse health effects resulting from their participation in the Vietnam conflict. Several suggestions are offered to combine this effort with the Agent Orange study, particularly if serious difficulties are encountered in determining exposure to Agent Orange while in Vietnam. Previous discussions of this attractive possibility by the Science Panel and members of Congress, however, have indicated real concern that such a "merger" may seriously compromise the Vietnam Experience study while adding little advantage for the Agent Orange study. The Science Panel recommends that the Vietnam Experience study be conducted essentially as designed.

C. Agent Orange Study

A number of criticisms and suggestions are offered for the successful conduct of an Agent Orange study. Most of these relate to potential problems with the selection of exposed and unexposed cohorts and the attendent misclassification; comfounding with other important and possibly health-related exposures while in Vietnam; and the lack of clearly defined health outcomes which can be investigated. All of these issues are inherent in any study of the possible long-term health effects of poorly recorded past exposure to toxic substances in a potentially dangerous environment. Furthermore, much of the information needed to make a sound judgement as to the appropriateness of the current design is not yet available. The Science Panel recommends a major reevaluation of the revised protocols after the selection of at least some of the units to be included in the high and low exposure cohorts. At that time, there should be sufficient information developed during the pretest and pilot phases of the studies to assess the feasibility of an Agent Orange study and the necessity for extensive medical and laboratory examinations.

V. Overall Objectives and Purpose of Investigation

Regardless of the stated objectives and purposes for various elements of the proposed studies of Vietnam era veterans, there are expectations which will be expressed during and at the completion of the studies which may not be fulfilled. It can be anticipated that criticism may be directed toward almost any objective scheme designed to assign an exposure index to individual veterans based on records contained within the Department of Defense. The choice of study subjects exclusively from the Army for both cohort studies is at least partly dependent on the expected availability and accessibility of such records. The descriptive nature of health outcome measurements is dictated by the general lack of concensus in the medical community of what to expect. Thus, some vagueness in the interpretation of results will be unavoidable.

The CDC is to be commended for their ongoing attempts to brief the public-at-large, especially the concerned veterans' groups and to provide opportunities for their suggestions and evaluations to be incorporated in the proposed studies at the outset. The Science Panel would like to encourage the CDC investigators to continue this policy and to thoroughly explain the capability of the proposed studies to fulfill legitimate but perhaps unreasonable demands of the veterans, the public and the Congress. While it may not be possible to obtain an unconditional endorsement, a clear statement of the limitations should help prevent misunderstandings of the objectives at the completion of the proposed studies.

August 3, 1983

Review of CDC Protocols for Epidemiological Studies of the
Health of Vietnam Era Veterans
Prepared by the National Institute of Environmental Health Sciences

The protocols for the proposed studies are well written and indicate an understanding of the problems which might be encountered. It should be pointed out that most of the suggestions discussed in this review are concerned with the difficulties inherent in studying this issue, particularly the potential health effects of exposure to Agent Orange while in Vietnam, rather than deficiences in the protocol development. It is anticipated that the CDC investigators will make appropriate adjustments in the procedures used to locate, recruit and interview prospective study subjects depending on results of the pretest and pilot phases of the studies. It is also understood that the full development of the interview instruments and examination procedures is an ongoing effort and will be completed during the pilot phase.

Vietnam Experience Study

The selection of study subjects from the personnel files at the National Personnel Records Center in St Louis should provide an unbiased sample with unambiguous classification of service in Vietnam. CDC intends to select Vietnam and non-Vietnam cohorts which are comparable in service-connected items such as time, branch, location and length of service. In addition, since the number of available records is so large, it should be possible to select subjects so that the two cohorts are also comparable in age, race, educational level and region of the country from which inducted into the service--factors which may contribute to current health status. This should enhance interpretation of any differences found in health status and is a simpler and more direct procedure than analytical adjustment for confounding by preexisting socio-demographic factors. Furthermore, the records of discharged Veterans from all branches of service are contained within the National Personnel Records Center and there is little reason to limit the investigation to Army Veterans

Most of the items indicated in the list of topics to be included in the interview and examination are relevant to a general assessment of physical and

mental health. However, the criteria employed to assign specific diagnostic categories, such as Post Traumatic Stress Disorder, should be incorporated early in the development of examination procedures. This should also include some estimate of functional disability as a readily understandable measure of health decrement which might be associated with service in Vietnam.

Agent Orange Study

Almost certainly, the major difficulty in conducting the Agent Orange Study will be the identification of cohorts which differ significantly in their exposure to Agent Orange and are similar in other aspects of their Vietnam experience--particularly combat exposure. The initial random selection of Battalions among those serving in III Corps may not include the most highly exposed and least exposed units. Some method should be chosen to enhance the likelihood of including these in the study. One such method may be to select units from among those known to be operating in heavily-sprayed and non-sprayed areas from overlay maps and other records if this is possible.

The random selection of one day per week to estimate unit exposure could easily miss very close encounters, and appears to be designed to minimize the substantial effort required by the AAOTF in recording daily locational parameters. An extension in time and distance out to 60 days and 8 kilometers, however, markedly increases the number of computer matches that will be required to select units while adding very little exposure for the more distant encounters. The combination of a more selective initial unit identification with fewer and closer categories of encounters may provide a better selection of highly exposed units. Apparently non-exposed units can then be checked at greater time and distances to verify their lack of recorded exposure.

Unfortunately, little of the information necessary to evalute exposure status is available at present, and must await the identification of units with high and low exposure. Thorough documentation of the procedures used and an attempt to evaluate the completness of application records should be maintained throughout the unit selection process in order to evaluate the apparent exposure status of units selected. A reassessment of the probable difference in exposure

between the high and low groups should be made at that time to determine whether an Agent Orange Study is feasible. In addition, there should be some assurance that Veterans, the public and Congress will agree or at least understand that an estimate of exposure developed in this way is realistic. This will be particularly important if there is found to be no difference in health status of exposed and unexposed cohorts.

During the design and implementation of the Ranch Hand Study, the Air Force Investigators argued effectively that U.S. ground troops in Vietnam were not excessively exposed to Agent Orange. It was on this basis that ground troops in Vietnam were not included in the Ranch Hand Study, as had been recommended by the National Academy of Sciences in their review. It is of the utmost importance, therefore, that units be selected to achieve the maximum separation between likelihood of exposure and non-exposure to herbicide in order to minimize misclassification of exposure status of the cohorts, while maintaining an otherwise comparable Vietnam exposure.

Most of the health effects thought to be related to herbicide exposure among occupationally exposed individuals are generally of short duration (except chloracne). It is thus not clear what additional information will be gained by examining individuals 15 years after possible exposure which cannot be determined from interview plus, perhaps, verification of medical diagnoses. An examination could be included at a later date if deemed necessary following preliminary analysis of interview data. Results from the Air Force Ranch Hand Study should also be consulted before the need for a medical and psychological examination relevant to herbicide exposure is finalized.

Soft Tissue Sarcoma/Lymphoma Study

This is a classic Case-Control design with the additional advantage of drawing cases from a defined population base. There are, however, a number of other studies which are addressing the possible relationship between Soft Tissue Sarcoma, Lymphoma and other cancers and exposure to dioxin contaminated products. The Armed Forces Institute of Pathology, for example, claims to have

access to approximately one third of all Soft Tissue Sarcoma cases in the country and there may well be considerable overlap. Also, the National Cancer Institute is currently conducting studies on the possible association between several of the cancers and herbicide and insecticide exposure. The possible association between herbicide exposure and Soft Tissue Sarcoma/Lymphoma is of worldwide interest, and it may be prudent to coordinate this effort with other agencies already working on this issue. This should enhance the proposed study and avoid possible duplication of ongoing effort.

General Comments

There is included in the protocols a large component of effort devoted to pretest and pilot phases of the various studies. It is also recognized that this activitiy is necessary to fully develop these studies and to provide a basis for modifying procedures. However, the present protocol does not include much detail on how the information obtained during these early phases will be utilized in further development of the studies. A more detailed description of how decisions are to be based on the results of pretest and pilot activities would enhance monitoring of the study as well as decision making by the investigators.

A final concern is with the exclusive use of Army Veterans in the two cohort studies. While it is recognized that this should increase the homogeneity of study subject characteristics and records and is thus less likely to introduce biases in the studies, it is not clear that results from these studies will be acceptable to all Veterans, the public and Congress. There may be some perception that different branches of the service were systematically more exposed--particularly Marine Corps veterans. The Veterans Administration has observed that a disproportionately larger percent of Marine Veterans are included in the Agent Orange Registry than Veterans from all of the other services. On the other hand, the AAOTF has determined that most of the Marine Corps unit records are inadequate for determining proximity of herbicide applications and are thus not suitable for inclusion in the Agent Orange Study. Some discussion of this should be provided and an assurance that this is acceptable to the community at large.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 29 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Dr. Carl Keller, Chairman Protem
AOWG Science Panel

SUBJECT: Review of CDC Protocols for Evaluation of Health of Vietnam Veterans

The EPA reviewers would like to preface their comments by first commending the CDC investigators for developing the protocols within a short time frame, and for tackling such a difficult problem. Additionally, EPA reviewers further appreciate the fact that due to a combination of constraints and the need to restrict the size of the draft protocol to a manageable size, that CDC investigators may not have had sufficient time to further elaborate and develop certain aspects of the protocol which either necessitated pilot study data or would have required extensive background documentation. The latter concern is probably particularly relevant to the work done by the AAOTF and the development of the exposure index. Therefore, the EPA acknowledges that many of the following comments may have already been given serious consideration by CDC investigators.

I. Background and Review of the Literature

Although the CDC literature review is relatively current and appropriately takes advantage of previous published comprehensive literature reviews, there is relatively little discussion of the clinical experience of the presently on-going veterans studies. Recent Congressional testimony by Dr. Custis of the V.A. stated that there have been over 350,000 Agent Orange related outpatient visits, over 100,000 physical examinations, approximately 20,000 veterans who have received more than one exam and about 9000 Agent Orange related hospital admissions (May 1983). Although the physical examinations of veterans conducted by the V.A. represent a self-selected group, they nevertheless may provide a valuable data base from which to refine and modify physical examination protocols as well as providing reviewers with a basis for evaluating the relative merits of individual studies.

EPA reviewers feel that much valuable data exists which could improve the design and conduct of the proposed studies. Those suggestions and sources of data which apply to the development of an exposure index and the selection of a highly exposed cohort are more appropriately discussed in the following section (II. Exposure Index). With respect to information which may influence the design of the physical examination protocols, it may be useful to determine what the actual prevalence rates are for certain abnormal conditions among the 84,000 veterans on the V.A. Agent Orange Registry (AOR) and then apply this data to the selection of specific examination procedures and power calculations of sample sizes. (Similar prevalence rates among self-selected groups were assembled by James Dwyer and the Citizen Soldier organization.)

With respect to data which is relevant to the soft tissue sarcoma survey the V.A. Office of Reports and Statistics assembles information on the estimated number of Vietnam Era Veterans by state of residence currently, in the recent past and at time of entry into military service. This data would allow CDC to calculate estimates of veterans likely to be living in SEER area registries and would provide guidance for concentrating follow-up efforts for the mortality studies. More importantly however, EPA reviewers feel that it would be desirable to include a general discussion of how the proposed studies relate to the other on-going efforts and why CDC feels that these studies would be more likely to yield information on the possible adverse effects of Agent Orange.

II. Exposure Index

Accurately classifying Vietnam veterans with respect to herbicide exposure is the single most important aspect of this investigation, and CDC appropriately described several reasons as to why these obstacles have been a "formidable impediment to the accurate assessment of health effects related to herbicide exposure" thus far. Nevertheless, CDC feels that the "Herbs" tape and other available records are sufficient to make a reasonable determination of a veteran's potential exposure to Agent Orange. It is not clear however, how the CDC intends to validate this exposure index.

EPA reviewers concur with both of the methods proposed by Dr. Jerome Bricker in his 4 December 1981 concept paper to the AOWG Science Panel. Basically his proposal consists of selecting a sub sample of "likely-to-be-exposed" veterans from the Agent Orange Registry (or some other source, such as AFIP registry), determining their battalion assignment, and then determining their herbicide exposure status.

The sub-sample of individuals could be selected (1) on the basis of the fact that they filed compensation claims or (2) because their questionnaire data suggest that they were likely to have been heavily exposed. It is expected that some military units would be likely to be reflected as having multiple claimants (or highly exposed) from the same units and that these units were within close proximity to aerial spray missions. Similarly, the units selected as unexposed to any herbicide spraying from either the ground or the air should have fewer claimants or individuals reporting heavy exposure. A similar method may be applied to the preliminary results of questionnaire data in order to assess the validity of self-reported exposure status.

Although there is still not a concensus among the scientific community concerning the significance of and most appropriate analytic procedures for measuring dioxin in adipose tissue, such data may be forthcoming after the American Chemical Society conference on dioxin this August. Measurement of dioxin residues by objective analytic procedures among individuals and battalions presumptively classified as highly exposed might provide the most unambiguous confirmation of exposure.

The second major concern with respect to classifying veterans by potential exposure status is to investigate the influence of all confounding exposures, particularly combat experiences and insecticide exposure. It would appear that the only efficient way to assess confounding exposures is to perform detailed medical and nonherbicide exposure histories after preliminary results suggest a potential health effect problem. Or conversely, if clusters of health effects are reported for non-herbicide exposed individuals, then other etiologic agents should be aggressively investigated among these battalions.

EPA reviewers also concur with those concerns expressed by Dr. Jerome Bricker and other researchers of the AAOTF intimately familiar with the data on herbicide exposure in Vietnam. Of particular concern, is the lack of sufficient rationale for randomly choosing one day of the 104 weeks and then determining individual exposure status. It would appear that there are alternative methods for ranking battalions and individuals by potential exposure that would ensure a broader separation between "likely" and "unlikely" exposed cohorts. EPA reviewers feel strongly about the need to somehow accomodate multiple exposures, such as those military

units which were temporarily located near areas which were recently sprayed. The currently proposed index simply offers no reassurances that the most highly exposed cohorts would be selected. This recommendation is discussed further under the Agent Orange study section.

III. General Study Design

With respect to the rationale and general study design, the case-control study of soft tissue sarcoma, the retrospective cohort mortality study, and the Vietnam experience study all represent needed additions to the current investigations of Vietnam veterans and appear to be relatively straight forward. However, the assessment of morbidity outcomes among Agent Orange exposed veterans is not as straight-forward as the above studies.

The utilization of a one-time physical examination and health questionnaire as the major instrument for assessing health status has certain limitations, such as (1) missing those individuals whose overt manifestations related to Agent Orange exposure 15 years ago may not have persisted until the time of examination; (2) secondly, missing those individuals who currently have no apparent physical manifestations of disease but may nevertheless have subclinical metabolic changes of medical significance which may not be adequately investigated during the exam; (3) and thirdly, some veterans may not yet have had sufficient time to develop signs and symptoms associated with Agent Orange exposure.

Pazderova et al (1981) reported on the development and progress of chronic intoxication by TCDD among 55 workers who had been engaged in the production of 2,4,5-T and later became ill. The description of the manner in which symptoms and disease developed in these men may provide some guidance in designing a physical examination and illustrate some of the concerns expressed above.

> "The first symptoms of intoxication which occurred at the time of exposure were: gradual, but rarely sudden, formation of chloracne, a feeling of sickness, fatigue; weakness in the lower extremities; and frequently, pain under the right coastal arch. In 10 patients, however, the first symptioms of intoxication appeared several months after work with TCDD was completed. The intoxication affected several organs

> and systems, ... the extent of organ damage was not uniform, ... and the severity of illness was not related to the duration of exposure, job status, or age." (p.6).
>
> Futhermore, "the progression of illness was not linear. In some patients, symptoms and signs of intoxication that were present from the very beginning of the illnes, became more severe during the 3-4 years that followed intoxication. In others, however, organs and systems that were functionlly normal during the beginning of illness later became impaired. Deterioration occurred suddenly, the eliciting factors sometimes being intercurrent illness, stress or unusual physical exertion. In other patients, however, deterioration could not be ascribed to specific factors, but was probably attributable to the spontaneous course of the illness proper. Deterioration and subsequent improvement did not occur occur consistently in individual organs and systems"

Although certain metabolic parameters remained pathologically abnormal, the health status of most patients was stable after five years and most biochemical measurements had returned to normal. These findings would suggest that although there is evidence that herbicide exposure produces long-term chronic effects, the likelihood of observing these effects in a one time physical examination 15 years after exposure is probably small; this is especially true if there is a potential for misclassification bias and a strong "healthy worker" effect overall. Therefore, it is for these reasons that EPA reviewers feel that the alternative approaches discussed in the Agent Orange section should be given serious consideration.

IV. Specific Concerns

A. Sarcoma-Lymphoma Study

With respect to the case-control cancer study, EPA reviewers had only four recommendations. As mentioned previously, it is strongly recommended that CDC investigate the current residential patterns of veterans to ensure the maximum probability of selecting cases with Vietnam service. Secondly, EPA reviewers suggest closer collaboration with other organizations conducting soft tissue sarcoma investigations and that all on-going studies be provided with CDC's questionnarire for assessing Vietnam service status. Additionally, serious consideration should be given to the

simultaneous investigation of other cancer sites potentially associated with dioxin, particularly liver cancer. And finally, since the most important risk factor in the case-control study (Vietman service with herbicide exposure) will ultimately be ascertained objectively and independently of the personal interview, EPA reviewers feel that selecting cases retrospectively and conducting next-of-kin interviews would be profitable.

B. Vietnam Experience Study

If the overall consensus among reviewers is that the cumulative influence of previously mentioned weaknesses outweighs the likelihood of detecting any potential adverse health effects among Agent Orange exposed veterans, then serious consideration should be given to refocusing the thrust of study. The new orientation would attempt to investigate adverse health outcomes associated with combat experience in general rather than simply using the "Vietnam experience" cohorts as a comparison group. Obviously, those cohorts selected for the Agent Orange study would still serve as the primary study groups for a more encompassing Vietnam experience study. The AAOTF could be instructed to select representative cohort battalions (i.e., artillery, engineering, and infantry) as well as a spectrum of time periods, terrain and known hazardous exposures. In essence, the random day selection procedure currently proposed by CDC actually satisfies these requirements at least for the III Corps between 1967 and 1968.

As an alternative method to the cohort approach (or in addition to the proposed cohort studies) the feasibility of utilizing the VA AOR and Patient Treatment File in a case-control approach should also be explored. The relative fraction of veterans with certain diseases who served near areas of herbicide exposure could be compared to other Vietnam era veterans as well as to those of other foreign wars. This approach has the advantage of investigating relatively rare conditions, such as porphyria cutanea tarda, while more efficiently utilizing pre-existing resources.

C. Agent Orange Study

With respect to reproductive hazards, EPA reviewers feel that the present investigation of structural abnormalities among veterans of the Atlanta area is insufficient to adequately investigate these problems. It would be desirable to investigate other reproductive related endpoints on a highly exposed cohort, such as the "chemical unit spayers" but EPA acknowledges the fact that the probability of detecting clinical indications of reproductive effects in the male veterans at this point in time is highly unlikely. Therefore, more consideration should be given to investigating the reproductive histories of veterans' spouses.

Overall, EPA reviewers are adamantly concerned with three aspects of this study. The first concern is that serious consideration be given to a thorough examination of a much smaller cohort who are most suspected of being highly exposed. This group would appear to be the "chemical unit sprayers" and the AAOTF said this group consists of about 800 to 900 men. Although there are problems of power similar to those confronted by Ranch Hand investigators, this group is the only cohort which is most likely to demonstrate physical and subclinical findings.

The inclusion of a vanguard group does not preclude a concurrent investigation of a much larger cohort, but EPA reviewers feel that this investigation should be primarily focused as a retrospective examination of health and interview data with five year follow-up analyses of selected morbidity and mortality endpoints. Using this approach, CDC investigators could satisfy veterans' and legislators' concerns by actually investigating a much larger cohort, both retrospectively and prospectively, with fewer resources.

Secondly, should CDC investigators continue to feel that physical examinations of a large cohort is indeed warranted on scientific grounds, then EPA reviewers strongly suggest that multiple examining centers be utilized and that a larger fraction of the 6,000 man Agent Orange cohort be examined. In addition, serious consideration should be given to five-year serial examinations. These serial follow-up exams could be of a

abbreviated nature, with the option of performing more sophisticated tests when indicated by physical findings or questionnaire data. Priority consideration should be given to examining the data on the AOR and the preliminary results of the Ranch Hand study for any guidance in designing the initial examination protocol.

With respect to the psychological batteries, EPA reviewers strongly recommend streamlining these tests. If possible, separate test batteries and hypotheses should be developed that would attempt to differentiate between combat related post traumatic stress disorder and those psychological conditions possibly associated with herbicide exposure. If this is not possible, tests should be selected and their results analyzed in such a way that guidance could be provided to the V.A. and legislative bodies for considering the reasonableness of war-related disability compensation. To report mere frequencies of various responses to psychological tests without anticipating their ultimate usefulness would not justify such a large fraction of time and resources as indicated in the proposed protocol.

And finally, with respect to the selection of the Agent Orange study participants, CDC is encouraged to reexamine their rationale for randomly choosing battalions from the universe of those battalions containing acceptable records, and then randomly choosing one-day of the week to ascertain battalion positions. EPA reviewers feel that these two stepwise procedures increase the opportunities for misclassification bias, and that alternative methods of ranking combat companies should be investigated.

DEPARTMENT OF THE ARMY
WALTER REED ARMY INSTITUTE OF RESEARCH
WALTER REED ARMY MEDICAL CENTER
WASHINGTON, D.C. 20012

IN REPLY REFER TO:

SGRD-UWH

12 August 1983

SUBJECT: Review of CDC Agent Orange Protocol

MEMORANDUM FOR CHAIRMAN OF SCIENCE PANEL, AGENT ORANGE WORK GROUP

Using the guidelines by the Subcommittee on Protocol Review, my comments are as follows:

1. Background/Literature Review: Adequate. I think the key here is to identify the hypotheses or questions to be answered, the outcome variables to be sought, and potential confounding variables. This is reasonably summarized in Appendices A & B and the protocol. The VA Registry would only be valuable for further hypotheses to check (i.e., another disease or organ system to check).

2. Exposure Index: This is the true achilles heel of a cohort design and the Agent Orange study could be in serious jeopardy or even impossible due to this. Troop exposure estimates are indirect and have many potential error sources. Supposedly the NAS validated the Herb tapes as fairly accurate but the science panel has not seen the report and the degree of accuracy is unknown. For example, to how many kilometers (or fractions) are the spray tracks accurate? How many recording errors are there in perimeter spray records or aborted spray runs? Certainly error exists -- but to what degree: 10%...50%? Independent confirmation (e.g., aerial photos) might help.

A second source of error arises from the troop locations. Records for units may be incomplete and some innaccuracy of coordinates is to be expected. Also of concern is the measurement convention that uses the Company Headquarters as the index of an individual's exposure. Individual troops will obviously range up to many kilometers from this point. Nor can the assumption of a straight line path from the previous HQ location be considered a reasonable assumption. Troops would rarely move in perfectly straight routes except in a chopper on a windless day. In that case they would not be ground exposures.

All the above sources of error are in addition to the "necessarily arbitrary" standards for estimating unit exposure (p. 26). Rather than three, one should be selected after some spray measurements are made and the best model selected to estimate distance and persistance. Again some idea of the variation would help provide an estimate of the misclassification risk.

Finally, one must consider the misclassification as "unexposed", those who had a significant civilian exposure. For most veterans, the year in RVN only represents 2-3% at most of their life experience considering the huge usage of these chemicals in the U.S.; surely many "unexposed" contracted TCDD at home.

All the above greatly increase the risk of misclassification and could significantly decrease the power of the study. Also such "misclassifications" tend toward decreasing the difference between those exposed and those not exposed. It biases towards the null hypotheses (and against the veterans). It would seem wise to estimate the effect of this cummulative error plus dropouts and non-respondents on the study power during the pilot studies. Also the decrease in power due to three rather than two cohorts needs to be considered. Then at some point, probably at the end of the pilot study, the study should be reviewed again. At that time, not only its validity but its utility as a guide to policy making five years from now should be assessed. If the cumulative problems make it unlikely to either convince veterans or help Congressional decision makers, it should be terminated.

Although there are many problems with a Vietnam exposure study, at least the exposure should be a fairly sound. In addition, a narrow causative agent, e.g., Agent Orange, would not be assumed and place all the vets' "eggs in one basket". If the veterans' complaints were due to some other agent and its magnitude significant, this would have a far greater possibility of finding it.

Finally, the question of confounding due to other chemical exposures cannot be adequately addressed for many of the same reasons as Agent Orange. Also, these exposures are also relatively unknown as to effect.

3. General Study Design: The basic designs are reasonable. I do not share the concern that non-persistant effects would be missed. These then are not health concerns nor do they justify compensation. Further, latent or subclinical concerns are too nebulous and really are best addressed by Ranch Hand. Testing is best reconsidered after a pilot study.

4. Specific Concerns: Most of these concerns pale in the face of exposure problems.

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D.C. 20301

HEALTH AFFAIRS
(HEALTH PROGRAM
EVALUATION)

21 JUN 1983

Carl Keller, DVM, MPH, Ph.D.
Chairman Pro Tem
Agent Orange Working Group Science Panel
National Institute of Health, Bldg. 31, Rm 2B55
9000 Rockville Pike
Bethesda, MD 20014

Dear Dr. ~~Keller~~ Carl:

As discussed in your Minutes of the Science Panel Meeting of May 31, 1983, a copy of the Draft Protocols for Epidemiologic Studies of the Health of Vietnam Veterans prepared by the Centers for Disease Control (CDC) has been received and reviewed by me.

In the overall sense I would say that CDC has done a tremendous job in developing the proposed protocols for the three studies. I am sure you know after all of our meetings together just how earnestly Mr. Dick Christian of the Army Agent Orange Task Force (AAOTF) and I want the proposed protocols to work and determine once and for all to the best of all of our abilities if there are effects to the veterans from Herbicide Orange. Because of this fervent desire and my detailed work with Mr. Christian on the mass of Army records I have some very serious concerns about one aspect of the selection of "likely exposed" and "unlikely exposed" troop cohorts as first described on page 23, subsections 3) and 4) at the bottom of the page of the protocol. To go back in time, from our many meetings down at the VA, I thought one of our basic premises was to develop a methodology so that we could be sure at the end of the records review and HERBS tape and Service HERBS tape comparisons that we had a group of men from many companies who had the maximum possible close proximity exposure possibilities for Herbicide Orange and in the second cohort by the same detailed day-by-day locational comparison we would arrive at a similar group (from the same Corps area) who had served in may combat companies an yet to the best of our research were not likely to have been exposed by virtue of the time and distance parameters which we had set up for the computer tape comparisons. For further background and I am not sure that CDC staffers fully know about this, the Ranch Hand missions for defoliation were not done on a random basis throughout the year. Basically, the Ranch Hand missions to be most effective had to hit the trees during their maximum growing period; therefore, the missions started in the north part of the country and more or less proceeded down southward through the country as the year progressed. Similarly

during the heavy rain season missions were restricted, hence in any one year period you did not necessarily have a normal or equal distribution of missions in a certain Corps area throughout the year or two year period. In the case of localized spraying of base camps and fire base perimeters spraying was more randomized in time as the objective here was to keep down the jungle growth to prevent intrusion by the Vietcong. Nevertheless, in their records research the AAOTF seems to have found a repetition period of about five weeks for perimeter respraying, And finally, in the case of large herbicide emergency dumps from battle damaged Ranch Hand aircraft we have a strictly random happening, but it does constitute a potentially very heavy herbicide exposure area (1 km. x 2 km. in size) for troops to be under or pass through.

With the above considerations in mind, the random sample selection of 50 battalions (250 companies) from among all battalions with acceptable records as called for in 3) of page 23 seems to defeat the purpose of finding those companies who have the highest possible exposure and those who have the least possible herbicide exposure during the two year time window. Here at this step it would seem that the AAOTF should do a day-by-day geographic locational analysis for 50 battalions who by map comparison to the Herbs tape plots for CY 1967 and CY 1968 operated in very heavily sprayed Ranch Hand areas. This should, based on our earlier battalion studies which showed a throughput of 2,300 troops per year per battalion, give a sample size of over 100,000 people per year. This would give you the battalions likely to have had heavy fixed wing delivery herbicide exposure. Similarly, the AAOTF would then go through III Corps battalions to find those who operated outside of the heavy Ranch Hand spray plots for those two years to select the battalions not likely to have been in herbicide sprayed areas. A day-by-day geographic locational analysis would also have to be performed and comparisons made by computer to determine if these operating companies were in fact (based on their records of operating locations) not likely to have been exposed to any Ranch Hand spray tracks. Finally all companies within all of the battalions could be ranked from highest exposure to herbicides to least or no exposure to herbicides. Random troop selections could then be made from the top and bottom of the scale of listed companies until the desired cohort samples were filled.

My most serious concern comes from item 4) on page 23 in which CDC then proposes to "abstract selected companies' locations on one randomly selected day of the week for each of the 104 weeks in 1967-78." As discussed earlier, spraying was not done on an even throughout the year basis. This method of selection of one day of each week would only cover 14.77 percent of the time of the exposure period. By chance you could find a company that on Monday, the day randomly selected, was many kilometers from a sprayed area; however, by Tuesday they could move into an area which had just been sprayed and then operate within this area for the rest of the week which would constitute a considerable exposure, and yet by the random day method you would come up with

that company not having any exposure for that particular week. The contrary also works as on the random day selected a company might be just at the boarderline of an exposed area but in the following days they rapidly withdrew from any contaminated area. By luck you might have a few units picked which were exposed to a high degree and a few units which were not exposed but my main concern is that in the great middle zone you would have a high likelihood of much misclassification as to actual exposure. This is the very thing which CDC wants so very much to avoid and so do I, but as I see it by this random, one day of the week selection procedure they would not greatly alleviate the AAOTF workload but would much more likely pick erroneous exposures of companies. Later then, in items 5) and 6), they would compare exposures by use of the HERBS and Service HERBS tapes and do a ranking of exposed companies. I believe that this could really give CDC a very erroneous exposure ranking by companies. It would surely be easier to do 104 comparisons per company than the entire 730 days of the two year period, but by no way would it be as accurate. We also should remember that the tour in Vietnam was only one year, hence the maximum number of days in the field looked at per individual would be 52 and not 365. During the other 313 days he could have had many opportunities to be exposed to herbicides either in the field or from perimeter spraying at his base camp.

If the intention of selecting just 104 random days, one in each week for the two year time window is to reduce the numbes of computer comparisons necessary against the two HERBS tapes and the time-distance weighting comparisons it would seem to me to be much better to go ahead and do laborious day-to-day geographic locations of each company selected from map comparisons and then to reduce the computer comparisons by "biting the bullet" and making a selection of what parameters in time and distance constitutes an exposure as we discussed in our many meetings together. In other words, do not go through all the many comparisons necessary to look at periods of post-exposure out to 30 days and distances from one to eight kilometers. They just are not going to be exposed if they were 8 km away from a sprayed area that was sprayed 29 days ago. My bet is that most of the troops will have received most of their exposures as to close time-and-distance criteria from perimeter spraying by helicopters, trucks, and hand spray apparatus. A few could have been heavily exposed if they were in an area which received an abort dump within the last day or so. However, the veterans are most concerned about the Ranch Hand spray missions and therefore these should be covered from a day-to-day time-distance proximity assessment for each and every day that the exposed or non-exposed service member served in Vietnam.

Reference page 26, second paragraph, which discusses the needs for various weighting schemes based on time and distance parameters up to 30 days and out to 8 kilometers. This paragraph states that relatively little is known about the environmental fate of herbicides and TCDD and even less is known about the human pharmacokinetics of these substances. As Lieutenant Colonel

Phil Brown and I advocated in several of our Science Panel meetings we do have a way to find out at least in a better way than we know now as to what happens to Herbicide Orange. We still have the C-123's with spray tanks in the Reserve unit in Columbus, Ohio. We still have a big test area out a Dugway Proving Ground in Utah. Why couldn't we run tests with Herbicide Orange out there on an instrumented aerosol sampling grid under worst-case conditions with no trees and a cross-wind condition to see just how much of the herbicide does go into tiny droplets and then how much is carried downwind and in what quantities? Then you would not have to guess as much when you try to establish a weighted exposure scale. Similarly tests could be run on helicopter spray apparatus, and from trucks and backpack sprayers. Further, why can't laboratory tests be undertaken to determine just how fast Herbicide Orange containing say 2 ppm. of TCDD is absorbed into leaves and plants and whether after absorption if any of the TCDD evaporates into the atmosphere. For that matter from a given quantity of Herbicide Orange contaiminated with TCDD sprayed onto a known area of soil in the heaviest concentration as might result from a low altitude full tank dump, test to see overtime just how much TCDD is aerosolized or is available with time for pick-up on boots or clothing. My understanding from verbal information recently received is that out Times Beach the dioxin is very strongly bound into the soil. Hence, what would be its availability for human absorption or inhalation in a damp jungle environment? Seems to me that this could be determined in some manner by laboratory experiments.

The following comments are of lesser significance, but were noted for possible change in the text of the draft protocols:

Page 24, 10th line of printing from top, "the relatively high level of TCDD contamination of the Agent Orange used then..." may be challenged as prior to 1964 agents containing 2,4,5-T were used and these were called Purple (Mean TCDD concentration of 32.8 ppm), Pink (Mean TCDD of 65.6 ppm) and Green (Mean TCDD of 65.6 ppm) which were much higher than the mean TCDD concentration of 1.98 ppm for Orange. As Young in his report points out 39 percent of all the TCDD was contained in Purple, Pink, and Green which was sprayed on 90,000 acres in Vietnam from 1962 to 1964. While Orange was sprayed on 3.5 million ares from 1965 through 1970, and contained a much lower mean concentration of TCDD.[1]

Page 28, third line from the bottom of the page, "If 55 companies each provide 150 suitable individuals this number will allow some loss..." My concern here is even though there may be 150 men in each 200 member company that would either be first term

[1] Young, A.L. et al, "The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and its Associated Dioxin.", OEHL Rpt TR-78-92, USAF Occupation & Environmental Health Laboratory, AMC, AFSC, Brooks AFB, Texas 78235, (Oct 1978), Ch. I, Pg. I-26.

enlistees or draftees, how many of these would there be who qualified as not being absent from duty due to battle wounds or diseases for a sufficiently long period to disqualify them from assignment to the combat company for the entire year period. The unit disease and casualty rates could be used to check out this point.

These comments are respectfully submitted for your consideration.

cc: Dr. Peter Beach,

ATTACHMENT A

Outline of General Concerns

I. Background and Review of the Literature

Although the CDC literature review is relatively current and appropriately takes advantage of previous published comprehensive literature reviews, there is relatively little discussion of the clinical experience of the presently on-going Veterans studies. Recent Congressional testimony by Dr. Custis of the V.A. stated that there have been over 350,000 Agent Orange related outpatient visits, over 100,000 physical examinations, approximately 20,000 veterans who have received more than one exam and about 9000 Agent Orange related hospital admissions (May 1983). Although the physical examinations of veterans conducted by the V.A. represent a self-selected group, they nevertheless may provide a valuable data base from which to refine and modify physical examination protocols as well as providing reviewers with a basis for evaluating the relative merits of individual studies.

1. Do reviewers feel that it would be desirable to include a more thorough discussion of all relevant on-going epidemiologic studies of veterans in the final protocol, especially the V.A. Agent Orange Registry examinations and any preliminary findings of the Ranch Hand study?

II. Exposure Index

Accurately classifying Vietnam veterans with respect to herbicide exposure is the single most important aspect of this investigation, and CDC appropriately described several reasons as to why these obstacles have been a "formidable impediment to the accurate assessment of health effects related to herbicide exposure" thus far. Nevertheless, CDC feels that the "Herbs" tape and other available records are sufficient to make a reasonable determination of a veteran's potential exposure to Agent Orange. It is not clear however, how the CDC intends to validate this exposure index.

1. Do the reviewers have any specific recommendations for validating the exposure index proposed by CDC (such as crosschecking the pilot study sample against yet another source of data or using a sensitive biological marker of exposure)?

   The second major concern with respect to classifying veterans by potential exposure status is to investigate the influence of all confounding exposures, particularly combat experiences and insecticide exposure.

2. Do reviewers have any recommendations for minimizing the influence of confounding exposures?

3. Do reviewers have any concerns or suggestions relating to the sampling procedures and potential selection bias posed by the proposed scheme for selecting study participants? For instance, what are the potential consequences of randomly choosing one day of the week and then selecting study participants from company records? Would it be desirable to estimate quantitatively the influence of misclassification bias in several hypothetical scenarios and then recalculate power estimates?

III. General Study Design

With respect to the rationale and general study design, the case-control study of soft tissue sarcoma, the retrospective cohort mortality study, and the Vietnam experience study all represent needed additions to the current investigations of Vietnam veterans and appear to be relatively straight forward. However, the assessment of morbidity outcomes among Agent Orange exposed veterans is not as straight-forward as the above studies.

The utilization of a one-time physical examination and health questionnaire as the major instrument for assessing health status has certain limitations, such as: (1) missing those individuals whose overt manifestations related to Agent Orange exposure 15 years ago may not have persisted until the time of examination; (2) secondly, missing those individuals who currently have no apparent physical manifestations of disease but may nevertheless have subclinical metabolic changes of medical significance which may not be adequately investigated during the exam; (3) and thirdly, some veterans may not yet have had sufficient time to develop signs and symptoms associated with Agent Orange exposure.

1. What is the cumulative influence of these considerations on the liklihood of detecting a true adverse health effect attributable to Agent Orange exposure? Would it be desirable to follow a subset of individuals for a longer period of time, with periodic examinations and updated questionnaires such as in the Ranch Hand study?

2. A consistent recommendation made by the National Research Council, the University of Texas and the Department of Defense Armed Forces Epidemiological Board in review of the Ranch Hand study was that the physical and neuropsychological examinations should be more refined by "evaluating a limited number of morbidity endpoints, each in greater details." Do reviewers feel that the clinical examination should be expanded further to include more sophisticated tests such as nerve conduction velocity or should the clinical examination remain broad scoped unless physical findings indicate more refined tests? Do reviewers have any other suggestions for improving the clinical examination protocol?

3. Do reviewers feel that it would be desirable for a more thorough discussion of the rationale for those tests whose purpose is not obvious, as well as a discussion of the criteria that will be used to evaluate the results of its pretests? Should the results of of the pretests be a major check point before proceeding with the rest of the investigation?

4. Do reviewers feel that the proposed timetable is overly optimistic?

5. What are the consequences on the power of study to detect potential adverse health outcomes if substantive modifications of the protocol are made during the course of the actual investigation?

6. Do reviewers feel that there needs to be a clearer delineation between the pilot study phase and the principal investigation?

IV. Specific Concerns

A. Sarcoma-Lymphoma Study

1. What is the effect of non-uniform histologic classification of soft tissue sarcoma, especially if non-SEER cancer registries are utilized?

2. Do reviewers have any suggestions for minimizing hypothesis testing problems posed by the simultaneous investigation of multiple cancer sites?

3. Are the power calculations of the ability to detect a statistically significant elevation of cancer risk based on appropriate data? For instance, does the protocol take into consideration the anticipated fraction of Vietnam veterans who were likely to have been exposed to herbicides between the years 1963-1969 and are now living within the boundaries of participating SEER registries?

4. Does the Committee have any recommendations concerning the selection of controls or minimizing recall bias among cases?

5. Could this study be conducted more efficiently and rapidly by closer collaboration with NCI and their investigations of soft tissue sarcoma? Alternatively, should all presently on-going case-control studies of soft tissue sarcoma utilize CDC's questionnaire for investigating Vietnam Agent Orange exposure?

6. What are the relative advantages and disadvantages of utilizing next-of-kin interviews of deceased cases, thereby offering the possibility of completing the study earlier than planned?

B. Vietnam Experience Study

1. Should this study be given more emphasis in view of its potential to investigate "many factors in addition to herbicide exposure which could have adversely affected those who served in Vietnam" as well as satisfying veterans' demands for an investigation of compensatable disabilities?

2. Do reviewers have any recommendations which could improve the ability of this study to investigate the morbidity of veterans who had combat experience but were not exposed to herbicides?

3. Do reviewers feel that there should be a discussion of how CDC's proposed Vietnam experience study relates to the "Vietnam Veterans Mortality Study" and the V.A. "Survey of Patient Treatment File for Vietnam Veteran In-Patient Care?" For instance, could the power of detecting conditions of low prevalence be improved by combining all three efforts?

C. Agent Orange Study

1. Do members of the Committee feel that the present on-going CDC investigation of birth defects, which is focused primarily on structural abnormalities, is sufficient to investigate all possible reproductive hazards? If not, would a more detailed questionnaire or spouse interview be sufficient to improve the investigation of reproductive hazards in the present study or would it be necessary to measure sperm count, morphology or sister chromatid exchanges to investigate adequately these endpoints?

2. Should there be a much more detailed discussion of the selection of tests for the neuro-psychologic examination? Would it be possible to describe a psychological syndrome or set of symptoms which have been reported most frequently by the V.A. examiners (and in the literature) and then investigate this "pattern" of symptoms more systematically?

3. Do the reviewers have any further recommendations that would improve the scientific validity of this study? For instance, does the Committee have any recommendations concerning the relative merits of CDC's efforts to balance misclassification bias against comparability of study participants?

4. Do the reviewers feel that the CDC is being realistic in their estimates of the number of physicals and specialist examinations that could be conducted by individual physicians? Is it absolutely necessary to examine all study participants at one or two centers, or could blood samples and test results be sent to a single laboratory for analysis, while at the same time examining many more veterans at multiple facilities? In order to minimize the inter-observer variation that multiple examining centers would present, would it be possible to develop strict clinical classification criteria or to document suspected cases of chloracne with photographs that could later be read by a panel of specialists?

5. Is there any way to include veterans who served multiple tours without compromising the comparability of the study participants or introducing too much selection bias?

V. Overall Objectives and Purpose of Investigation

It is clear that the major impetus for the current mandate by Congress (Public Law 96-151) to require the Veterans Administration to conduct an epidemiological investigation of U.S. veterans derives from the persistent and legitimate demands of veterans' organizations that the U.S. government investigate their claims for war related disability compensation. Although statements of purpose such as "to assess the possible health effects of exposure to herbicides and dioxin during the Vietnam experience" can certainly be understood to encompass the development of a data base from which such claims may be evaluated, the stated objectives of the CDC protocol do not reflect full cognizance of the potential problems of interpretation and litigation that are likely to follow a study of such complexity and controversy as this one. For instance, Representative Thomas A. Daschle has sponsored a special service-connected disability compensation bill which contains a sunset provision to retract the presumption of association for chloracne, porphyria cutanea tarda, and soft tissue sarcoma if data from the ground troops study does not confirm these associations. It would appear then that there are expectations, which although legitimate may be unreasonable, and it may be necessary to evaluate the objectives of the proposed studies within this context.

1. Do reviewers feel that the proposed studies, either individually or collectively, are sufficient to adequately resolve compensation issues? Are there potential modifications which could improve the ability of this study to resolve such issues?

2. With respect to the stated objectives, will the proposed studies contribute substantively to our understanding of the adverse health effects of 2,4,5-T and dioxin exposure among veterans?

APPENDIX D

CENTERS FOR DISEASE CONTROL AD HOC

REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date July 8, 1983

From Deputy Director for Research, EPO

Subject Review of Protocols for Epidemiologic Studies of the Health of Vietnam Veterans

To David Erickson, D.D.S.
Chief, Cancer Branch, CDD, CEH

A committee consisting of myself, Richard Dicker, M.D., medical epidemiologist, EPO; Dave Culver, Ph.D., Hospital Infections Program; and Claire Broome, M.D., Chief, Respiratory and Special Pathogens Branch, has reviewed three protocols for epidemiologic studies of the health of Vietnam veterans. Each of the three committee members, other than myself, prepared a separate written report, all of which are appended to this summary of our discussion of the protocols.

Overall, the committee commends the designers of these three protocols for their efforts with some extremely difficult problems. We believe that the studies have a good chance for success. What we are intending to do is to offer some constructive critique which may increase the likelihood that the studies will yield useful and valid information. We urge the investigators to take our comments as suggestions rather than concrete "musts." We recognize that the investigators may have considered some of our suggestions but have not included discussion of them in the protocols for lack of space. However, we do think they are important and suggest that the investigators perhaps might wish to consider them again.

Probably the major concern of all four of us was measuring the exposure to Agent Orange. Perhaps this was best stated on pages 9 and 10 of Richard Dicker's review. The committee strongly supports the concept of attempting to reduce misclassification of exposure to Agent Orange by attempting to determine each soldier's exposure, rather than each company's exposure. We recognize that this will introduce considerable difficulty. However, the resulting increase in certainty of classification may well be worth the effort.

Along these lines, we recommend, if possible, computerizing the location data of the 250 companies for every one of the 104 days. In this way, exposure scores could be calculated by computer for every soldier every day. It is unclear to us what increase in work this recommendation entails. However, we do urge the study managers to reconsider it because of its major benefit to reducing exposure misclassification.

Another problem with regard to exposure to Agent Orange is independent verification of whether the pilots dropped the Agent where the military

records state that they dropped it and the accuracy of the spraying i.e. could meteorologic conditions substantially alter the distribution for a given flight. In this regard, interviews with pilots and perhaps some data on how spray distribution from an airplane might help further refine what areas and, hence, who, was exposed to Agent Orange.

Exposure to Agent Orange also comes up as an issue in the sarcoma/lymphoma study. The power curves for these two studies are calculated on the basis of exposure to Vietnam, not exposure to Agent Orange. Presumably, only a fraction of the 15 percent of the military population who were exposed to Vietnam were exposed to Agent Orange. We were unable to find an estimate of the fraction of military personnel exposed to Agent Orange. Even if the investigators have to give their best guess at this, they should do so and incorporate this estimate into the sample size considerations for the sarcoma/lymphoma study.

The operation "Ranch-Hand study" which the Air Force is currently conducting must have much information on validity of exposure to Agent Orange. We strongly urge the investigators to review this carefully and perhaps alter their study design if the results of this Air Force study suggests that exposure to Agent Orange is even less accurate than the investigators suspect. One way to make up for this would be to increase the sample size.

Another specific concern of the committee was that in the Agent Orange study, Group 3 would come from non-combat, non-sprayed areas and, as the investigators note, might not be comparable to Groups 1 and 2, who are combat batallions from high and low sprayed areas. The committee suggests that it may be possible to develop an alternative third study group which is in combat, but non-sprayed areas. It would probably mean piecing together smaller units, and this would necessarily entail more difficulty in record review. However, it would increase the comparability and help to make the comparison of sprayed versus non-sprayed combat troups more easily interpretable.

The committee questions the investigator's acceptance of the military's belief that people were assigned to Vietnam or other areas on a random basis. We are extremely skeptical that this would be the case, and urged the investigators to look into this issue further. If there were some systematic biases in how soldiers were assigned to various areas in the world, based on their health, socio-economic status or race, this could markedly affect their outcome in the Vietnam Experience study.

The Vietnam Experience study could be made much larger. If, for example, Agent Orange had no impact, then all 24,000 subjects could be used in the Vietnam experience study in a straight-forward way. Even if Agent Orange had an impact, this effect could be considered, using a logistic-regression approach, and, all subjects used in the Vietnam Experience study. (See Dave Culver's discussion)

We discussed the subjectivity of outcomes. Clearly, the hardest data for the Vietnam Experience study, and the Agent Orange study, will come from the physical exams and examination of medical records. We strongly support the flexible approach outlined by the investigators which would allow modification of the study as it goes along, if results dictate such modification. However, the committee thinks that the investigators would do well to consider increasing the amount of objective information they get such as physical exams, and medical record review, and get this information early in the study. We think that 6,000 is really a small study size. If only 2,000 really have objective information (i.e., physical exams), this may prove to be insufficient. A comparison of the objective and subjective responses may suggest a major modification of the study as it goes along. Along these lines, we urge you to err on the side of collecting more information rather than less. Your hypotheses may well develop and change as you go along and it is easier to not have to go back and re-examine people and records.

Again, because we believe your sample size is minimal, we urge great effort to ensure high participation. Such efforts would be money well spent.

Of all the variables that intervene between the Vietnam experience and when outcome is measured in the 1980's, illicit drug use is the one that concerns the committee the most. Any of a number of intervening variables from the time of Vietnam experience to measuring the outcome can alter the results. It is likely that some of these, particularly, illicit drug use, may well be linked to exposure to Vietnam as opposed to exposure to other military duty stations. We would urge the investigators to talk in more detail to people who are investigating the epidemiology of illicit drug use in an attempt to define the most accurate way to determine this exposure. Again, objective measures that come from physical exams may prove to be the most useful. Medical record review of hospitalizations between Vietnam and now may also prove to be useful. This is such an important intervening variable that increased effort to accurately identify it may well be justified.

If the sarcoma/lymphoma study turns out to be too small, it may be well to expand into non-SEER tumor registries as the investigators suggest. The committee suggests contacting Dwight Janerich concerning the New York State (including New York City) tumor registry, as well as Brian Henderson concerning the Southern California tumor registry. These two registries alone could double the size of the proposed study.

The sarcoma/lymphoma study can be considered in two frameworks: first, as a study of sarcoma and lymphoma in the general population; and second, the study of sarcoma and lymphoma in Vietnam veterans. In the first case, it would be

well to include people even older that the group that the investigators plan to include. Since the disease is common in older people, one could determine with accuracy and power what are the key risk factors for the disease. One could then look to see in the subgroup who served in Vietnam, if these same risk factors are operative. It might then be easier to determine whether Agent Orange is a risk factor.

Howard W. Ory

Howard W. Ory, M.D.

Attachments

JUL 1 1 REC'D

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date June 30, 1983

From Chief, Statistics and Computing Activity
Hospital Infections Program, CID

Subject Review of Protocols for Epidemiologic Studies of the Health of Vietnam Veterans

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

Designing appropriate studies to assess the long term health effects of service in Vietnam is clearly a difficult task. The scientific problems encountered in deciding upon specific study objectives, study designs, sampling schemes, factors to be measured, etc. are numerous, not to mention the logistic problems for which strategies must be developed for locating subjects, conducting interviews, etc. and the preliminary thought that must be given to the analytic problems that are certain to arise in attempting to draw conclusions from the data. With the obvious concern of Vietnam veterans and their families, and widespread interest in the public health impact, the design of these studies and the conclusions drawn from them are certain to attract widespread attention, close scrutiny, and varying degrees of acceptability. The investigators are to be commended for the effort that has been expended so far. Attention must be focused during the design and data collection phase on being certain that the most appropriate subjects are selected for inclusion in the study and that sufficient information, of the highest quality possible, be collected on each of these subjects for answering the multiple questions that form the objective of the studies.

I foresee four general problems in conducting these three proposed studies or variations of them. All four of these problems are interrelated. First of all, Vietnam veterans have many concerns regarding health effects of their service in Vietnam. They are conjectured to be at increased risk for a variety of diseases as a result of their military experience. As the authors point out, no strong hypotheses are available at the outset of this investigation. Controversy swirls around the discussions of dioxin. Even if the proponents of its extreme toxicity are correct, any number of adverse health effects have been suggested as resulting from exposure to it. Rightfully so, this has prompted the investigators to design three studies, in the first two of which a broad spectrum of measurements on the health of Vietnam veterans will be obtained. Medical, psychological, and laboratory workups will be done. The multiplicity of response variables to be investigated for the possible impact of Vietnam experience in general and Agent Orange exposure in particular makes the studies difficult, but the sheer number of potential dependent variables is not my major concern. Rather, I am concerned that when the subset of health outcomes that appear to be adversely influenced by experience in Vietnam or AO exposure are identified the investigators may find that an inadequate amount of information has been obtained from the respondents regarding these particular health outcomes. Multiple manifestations of the disease, severity of illness, time of onset, duration, concomitant illness, etc., are all areas that would be explored in

greater depth in the data collection phase if the scope of health outcomes that must be studied were not so broad. In designing the interview instruments and laboratory tests to be performed I would suggest to the investigators that they adopt the principle of "if the information is potentially useful, then get it." While this principle is generally applicable, these studies would seem to require its adoption even more than is generally the case. I suspect the sample sizes of each cohort (6,000 interview, 2,000 lab) will prove to be insufficient for answering all of the questions that will have been posed and will be suggested by the data.

My second general concern is regarding the time lapse between 1967-68 and 1984-85. It will be difficult to link adverse health outcomes experienced today to events of 17 years ago, particularly in light of the anticipated incidence levels and conjectured levels of increased risk.

My third concern is for the multiplicity of factors that may have influenced each of the health outcomes to be investigated in these studies. While it will be difficult to obtain accurate estimates of AO exposure for individual subjects, at least that major risk factor of interest is well defined. The general Vietnam experience risk factor is more nebulous. Various measurements must be obtained to quantify this factor of interest. Beyond the measurements of these "treatments" I am greatly concerned about the multitude of other factors that certainly influenced the various health outcomes. Some of these co-factors will have to be identified and their influence removed before one can hope to have estimates that are even approximately unbiased for the impact of the risk factors of interest (AO/VE). This of course is the confounding problem. Others must be identified and their influence eliminated in order to obtain standard errors small enough to draw strong conclusions, or possibly any at all, regarding the influence of the risk factors of interest. Still other influences may serve as mediators for the influence of AO/VE. Agent Orange may only have had an adverse health impact upon veterans of a given race or the Vietnam experience may only have produced adverse health outcomes in the presence of a high level of drug usage during or after the Vietnam experience. While the analytic difficulties that will be encountered in attempting to draw conclusions from the data of these studies will be challenging, no skill or sophistication in the analytic phase will save the studies if inadequate information has been collected on at least the major influences of the various health outcomes. Once again the principle enunciated above should guide the investigators in designing the data collection procedures.

Finally, the quality of the data, veracity of responses, or in polite terms response bias is of concern to me. Clearly the time lapse from 1967 to 1984 makes collecting information on occupational experiences, combat experience, lifestyle, etc., in Vietnam difficult. The interviewing of respondents by telephone, the personal nature of some of the questions such as drug usage, the potential fear of the Federal Government on the part of respondents, etc. all have me concerned for the truthfulness of the responses that will be obtained.

In the Agent Orange study I agree with the need for three cohorts. The survey population, sampling frames, and methods of selecting the samples all seem reasonable. On each subject in cohorts 1 and 2 I would be sure to collect, as well as possible, information on his presence in his company on each of the 104 days. The investigators indicated that they would then calculate an index of AO exposure for each subject. I would most certainly strive to calculate such an index as well as an index of combat experience for each subject. Once the 50 battalions are selected, will the position of the 250 companies on each of the 104 days be computerized? Will the scoring of company AO exposure be done by machine? I assume so (and hope so) but the investigators didn't specify. With regard to the herbicide data, is there any way of obtaining information on the TCDD contamination level of each Agent Orange lot? I doubt it or the authors would have planned on using it, but it would sure be nice to know the TCDD contamination of the Agent Orange used in each Ranch Hand mission.

With regard to the Vietnam Experience study, I have one major suggestion. As currently planned, the Vietnam Experience study will consist of a comparison of the health experiences of the men in 2 cohorts, each numbering approximately 6,000 subjects. There are apparently no plans to use the data collected on the 18,000 subjects in the AO study in assessing the general impact of the Vietnam experience. Very detailed information will have been obtained on each of these 18,000 men both in terms of health outcomes, exposure to risk factors during and after Vietnam, etc. I would certainly use these 18,000 subjects and the information collected on them and compare them with the 6,000 non-Vietnam veterans from the United States, Europe and Korea. I think the investigators need to think this problem through more thoroughly. I would collect nearly identical information in both the AO and VE studies. If Agent Orange does not prove to be a significant risk factor for increased illness then attention in the investigation will focus on the general impact of the Vietnam experience. In this case, the selection of non-Vietnam veterans who, as a result of the luck of the draw, ended up in the United States, Europe, or Korea seems like an ideal choice for the comparison cohort. However, 6,000 may be too few for this cohort. I strongly endorse the design flexibility suggested in these protocols. The authors anticipate a need to modify the interview instruments and laboratory procedures during the course of the investigation as preliminary analyses become available. I think it important that the investigators plan on increasing the cohort sizes where necessary.

In the sarcoma/lymphoma study, the chances of success seem slim. Unless the general Vietnam experience has rendered its veterans to be at substantially increased risk of these cancers, I doubt that conclusive results will be drawn. Once again, there appear to be too many additional influences on the risk of these cancers. Presumably out of a desire to obtain incidence estimates, the investigators have imposed no restrictions except draftable age on the control group. Furthermore, the size of the control group is relatively small (1,800).

At this stage of the investigation, the investigators have properly devoted most of their efforts to the design of the studies and the logistics of collecting the data. Although the total size of the resulting data base will still be reasonably small, the data base development, data base management, and statistical inference tasks will still be formidable. I suspect the timetable estimates for this stage of the studies will prove to be gross underestimates. Our experiences in the SENIC project have helped us to discover some useful principals, standards, and plain old fashioned tricks in these areas. I would be most happy to share them with the investigators at the appropriate time.

Dave

David H. Culver, Ph.D.

Review of
PROTOCOLS FOR EPIDEMIOLOGIC STUDIES OF
THE HEALTH OF VIETNAM VETERANS

INTRODUCTION

The protocols for epidemiologic studies of the health of Vietnam veterans come in response to widespread concern among veterans, their families, Congress, and others about the potentially adverse health effects of veterans' exposure to the herbicide Agent Orange. This herbicide, used extensively in combat areas of Vietnam between 1967 and 1969, has been reportedly associated (or is suspected of being associated) with a variety of health effects, including chloracne, porphyria and other liver disorders, neurologic abnormalities, psychological and non-specific constitutional complaints, impaired immunological response, soft-tissue sarcoma and lymphoma, and adverse reproductive effects. The proposed studies are designed to investigate all the above outcomes except birth defects, which is already under investigation in a separate study.

Five related studies have been proposed: (1a) Agent Orange Mortality, (1b) Agent Orange Morbidity, (2a) Vietnam Experience Mortality, (2b) Vietnam Experience Morbidity, and (3) Sarcoma/Lymphoma Incidence.

I will first address the design of each of these studies separately, then address them as a group. In the assessment of each study I will concentrate on the object of that study, the conceptual and empirical outcomes of interest, the conceptual and empirical exposure contrasts of interest, the base population (subjects to be enrolled), and the appropriateness of each in relation to the others. I am limited in this task by two factors. First, I have no particular subject matter knowledge beyond what is presented in either the biologic aspects of the exposures and outcomes, or in the conduct of the military. Second, as the authors point out repeatedly, there are few hypotheses based in a priori knowledge of biologic plausibility on which the study designs can (and should) be secured.

Richard C. Dubes

AGENT ORANGE MORTALITY STUDY

Object - effect of Agent Orange on subsequent mortality

Outcome
- conceptual entity - death within a given time frame
- conceptual scale - yes/no
- empirical scale - yes if documentation of death by certificate, VA record, etc. (cause of death from hospital recrods)
  no otherwise
- appropriate? (ie, does empirical reflect conceptual?) - OK if good ascertainment of death; may be biased if differential ascertainment of death between exposure groups.
- note - If conceptual entity is specific cause of death, then problems may arise due to ascertainment as above, and with competing causes of death.

Exposure
- conceptual contrast - AO vs. $\overline{AO}$ (or TCDD vs. $\overline{TCDD}$)
- empirical contrast - "likely exposed" vs. "likely not exposed", ie, Group 1 vs. Group 2+3
- appropriate?
  - re: conceptual contrast - major problem is with misclassification (to be addressed later)
  - re: comparability of populations (selection bias) - Groups 1 and 2 are quite comparable. Group 3 is not. It would be much more desirable to restrict Group 3 to combat troups, if at all possible, from areas without AO spraying. The authors suggest that this may not be possible, but stratified analysis would be. Alternative possibilies, for Group 3 such as expanding the time frame to 1966-71, would also hamper comparability. Like the authors, I would find it difficult to interpret "high-high-low" findings.
  - re: comparability of extraneous effects - Are other exposures inextricably linked with AO exposure? This question requires knowledge of spraying methods, effect of spraying on vegetation which, in turn, may affect health, etc. Similarly, this study cannot disentangle the effect of TCDD from those of 2,4-D and 2,4,5-T without very specific information about these components. This issue is important in etiologic research, but less important in descriptive epidemiology.

Base Population
- -male Army draftees and single-service enlistees, non-officer, 1 tour only in Vietnam fully within 1967-8
- -absent from unit less than 90 days
- -St. Louis record available
- -IRS or NCHS/SSA/VA documentation of alive/dead
- -Group 1+2: combat battalion III Corps, adequate location records, at top and bottom of presumed-exposure ranking
- -Group 3: units in non-sprayed areas

Base Population (continued)

appropriate? - presumably. Only question concerns those who cannot be located at all, presumably a very small number. However, this could lead to outcome-dependent membership into the cohort, which could bias the study.

AGENT ORANGE MORBIDITY STUDY

Object - effect of Agent Orange on delayed or chronic morbidity

Outcome
conceptual entity - (various)
conceptual scale - yes/no
empirical scale - unknown presently, presumably mostly based on interview data (some on H&P and lab results)
appropriate? - OK if information is comparable between exposure groups, and if the empirical scales developed for the different diseases adequately reflect the conceptual scales. Data from the interviews alone may reflect self-diagnosis or concern about disease related to AO exposure, but the data from the exams should not be biased in this way.

Exposure - same as Agent Orange Mortality Study

Base Population
-same as Agent Orange Mortality Study, plus
-locatable
-consent to participate

appropriate? - The concern is always over the non-locatables and refusers, and in particular if they are differentially distributed over exposure status. This problem is recognized and adequately discussed by the authors. As also pointed out by the authors, subjects may be particularly difficult to enroll in the exam subgroup. If this turns out to be a real problem, affecting either validity or efficiency (power) of the study, a mobile exam center ("office on wheels") may help.

VIETNAM EXPERIENCE MORTALITY STUDY

Object - effect of Vietnam duty on subsequent mortality

Outcome - same as Agent Orange Mortality Study

Exposure
conceptual contrast - nebulous (to me, at least)
empirical contrast - US+Vietnam vs. US only/US+Korea/US+Europe
appropriate?
re: conceptual contrast * extraneous effects - For any sort of etiologic inference the conceptual contrast, or actually whatever it is that the emprical contrast is really contrasting, would have to be better defined. For descriptive purposes, however, it is less critical to do so.
re: comparability of populations - Although the authors have been told that assignment was basically a random procedure, assignment was also based on needs for skills and troop strength, which constantly changed. It is therefore critical to control for a variety of potential confounders. This may be problematic for veterans already dead at the time of the study.

Base Population
-St. Louis record available
-Army draftee or single-term enlistee, non-officer, served in 1966-1971
-US only or +Vietnam only or +Korea only or +Eurpoe only
-documentation of alive/dead

appropriate? - presumably. Again, non-locatables resulting in outcome-dependent membership is a potential but probably not serious problem.

VIETNAM EXPERIENCE MORBIDITY STUDY

Object - effect of Vietnam duty on delayed or chronic morbidity

Outcome - see Agent Orange Morbidity Study

Exposure - see Vietnam Experience Mortality Study

Base Population
-same as Vietnam Experience Mortality Study, plus
-locatable
-consent

appropriate? - see Agent Orange Morbidity Study

SARCOMA/LYMPHOMA CASE-CONTROL STUDY

Object - potential oncogenicity of Agent Orange in man, re: soft-tissue sarcoma and lymphoma (This is presumed primary object. Other exposures constitute important seconadary objects.)

Outcome
conceptual entity - soft tissue sarcoma; lymphoma
conceptual scale - yes/no
empirical scale - yes if SEER registrant
no otherwise
appropriate? - OK as such only if AO is a relatively non-specific carcinogen, that is, if it is related to all lymphomas rather than to a specific sub-type. In the latter case, only histologically-specific analysis would be appropriate. Unfortunately, the numbers will get very small.

Exposure (for primary object)
conceptual contrast - AO vs. AO
empirical contrast - "likely exposed" vs. "likely not exposed"
appropriate?
re: conceptual contrast - misclassification, as with Agent Orange Mortality and Morbidity Studies
re: comparability of populations - Obviously, this contrast would be best served by restricting the analysis to Vietnam veterans, at least as the comparability of populations is concerned. Even so, all the concerns about comparability among the veterans in the AO Studies apply here as well.
re: comparability of extraneous effects - Again, restricting to (or at the very least, stratifying for) Vietnam exposure will help, but the cohort studies may provide further insight into important potential confounders.

Study Base Population
-male, born 1933-1953
-resident of SEER area at time of study
-new case sarcoma or lymphoma OR
selected by random digit dialing (have telephone) and located
-agree to participate

appropriate? - presumably OK, unless sarcoma/lymphoma is related to socioeconomic status or other determinants of having a telephone, or if there is differential enrollment by exposure status.

Note
The incidence figures in Table 2 are from 1973-1977. The current "epidemic" of Kaposi's Sarcoma will undoubtedly result in much higher numbers of sarcoma cases, at least if the epidemic continues. While this may facilitate etiologic research into Kaposi's sarcoma specifically, it may not faciliate etiologic research directed to Agent Orange if the two are unrelated. In fact, it may hinder these efforts if resources are limited.

Note 2

Perhaps more than any of the other studies, this study can provide an unprecedented amount of information of considerable scientific interest, although not of direct interest to those interested only in the health effects of Agent Orange or Vietnam duty. It could be argued that these secondary objects of this case-control study are just as important to veterans as is Agent Orange, since they share most if not all of the potential risk factors for sarcoma and lymphoma as are present in the general public. If this argument is valid (it is to me), then limiting the study to men born between 1933 and 1953 is a disservice. The peak incidence of sarcoma and lymphoma is much later in life, and inclusion of a broader age range of subjects would allow for inclusion of many more cases, resulting in much more power to explore these other risk factors.

CATEGORIZATION OF AGENT ORANGE EXPOSURE

Characterization of Agent Orange exposure is perhaps the most important and difficult issue addressed in these protocols. The authors clearly recognize this, and devoted 10 pages (p.21-30) to a description of the method of classifying companies. Yet only the last two sentences of this description (p.29-30) mention classification of the individual subjects, which, to me, is the truly critical issue.

The method described by the authors is basically a "quick-and-dirty" one, of correlating unit location and spraying location on a randomly selected day each week, and assigning a weight or score. I presume that the more definitive approach of correlating locations on every day between 1/1/67 and 12/31/68 was considered by the investigators to be too wasteful of time and/or resources. An alternative "quick-and-dirty" method of selecting the same day each week (say, Tuesday) was not discussed.

The selection of a random day each week introduces more random misclassification than would the selection of the same day each week, but the time categories given on p.27 further compound this problem. In a 2 week period, days 1 and 14 could be selected at random. If a company stayed in the same location all 14 days, and were sprayed directly on day 7, the true exposure geometric score would be 16x4, integrated over time. The calculated score would be (2x4)x2=16. Any unit movement would further reduce the score.

The widest spread between random day selected and day of greatest true exposure in a 2 week period is 6 days. A 6-day spread could really have been a "direct hit", while a minimum 7-day spread in a 2 week period could not. Therefore, I suggest that if the random day approach is used, that the 4-30 day category be broken into 2 categories: 4-6 days, and 7-30 days. This would reduce some misclassification. Similarly, if feasible (and I don't know if it is), the distance categories could be constructed to separate the amount of movement in 6 days still consistent with a "direct hit" vs. distances inconsistent with such a hit.

As mentioned above, selecting the same day of the week reduces misclassification, since the maximum spread between day examined and day of greatest true exposure is only 3 days. However, a systematic bias could be introduced if spraying and/or unit movement were not distributed similarly for different companies. Military authorities might be able to provide insight into these matters and allow the investigators to choose the better system for selecting days. Overall, the strategy outlined in the protocol seems sufficiently sensitive to provide adequate separation of "likely exposed" companies at the top and "likely not exposed" companies at the bottom.

These considerations of company exposure pale in importance when compared to consideration of an individual's exposure. While the strategy outlined is acceptable for ranking company exposure, it is not acceptable for specifying an individual's exposure. The quick-and-dirty approximation should provide decent separation of "likely high" and "likely low" exposures, but in the simplest 2x2 table each subject must be classified by his own exposure characterization. It is essential that each subject's exposure to Agent Orange be characterized as specifically as possible, given the ackowledged limitations of the various records. Failure to do so will assure misclassification (perhaps random, perhaps differential), could quite possibly lead to spuriously negative (or spuriously positive) findings, and in the former case invites charges of "government cover-up." Since the biologic importance of intensity, duration, cumulative effects, etc. of exposure to Agent Orange is unclear, it seems desirable to develop and test a variety of composite exposure variables. However, all composites must be based on each subject's daily exposure or incidence of exposure to each spraying. It seems essential, therefore, that for every day a particular subject was in Vietnam, his location should be correlated with location of spraying, likely intensity of exposure, type of herbicide sprayed, etc. These daily or incidence exposure records can then be aggreagated and analyzed in whatever ways the investigators deem biologically reasonable.

SUMMARY

The proposed studies, in conjunction with the ongoing birth defects study, the Ranch Hand Study, and others, should provide as clear a picture of the health effects of Agent Orange exposure during the Vietnam conflict as is possible. Each study's design appears to precisely address the primary object of that study, and, in the Sarcoma/Lymphoma Study, many important secondary objects as well. The studies also complement each other quite well, providing a depth and scope impossible to acheive with a single study. Given imperfect information in an imperfect world, the proposed studies represent state-of-the-art epidemiology, and will set new standards against which other studies in the future will be compared.

I have not tried, in my review, to point out the many excellent features of the studies. In fact, the consistently high quality of the studies made it fairly easy to identify where potential problems lie. The authors themselves identified and discussed most, if not all of them. As listed below, some are potential problems only, some are inevitable given the realities of the Vietnam conflict, and some are due to man's limited knowledge.

1) Lack of a priori hypotheses makes study design difficult and increases the reliance on data-genrated hypotheses. The authors have wisely adopted a timetable for preliminary analysis and a flexible attitude toward data collection, allowing them to explore new hypotheses as they arise from this study and concurrent ones.

2) Misclassification of Agent Orange exposure was discussed above. While the records themselves are imperfect, inadequate characterization of each individual's exposure will only dilute further the strength of the studies and the credibility of the findings.

3) The third cohort of the Agent Orange Study may not be comparable to the others, since they differ in combat categories, combat experience, etc. Alternatives, such as broader time frame, inclusion of combat troops from more than one non-sprayed area, etc. should be at least considered.

4) Nonparticipation rates in the examination subgroups may adversely affect power and/or validity. The pilot or pretest phase should give some indication of the magnitude of the problem.

5) The small numbers of specific histologic types of sarcomas and lymphomas may make it difficult to draw etiologic inferences about Agent Orange. On the other hand, this study will likely

provide a wealth of information on other risk factors shared by Vietnam veterans and non-veterans alike. If these other risk factors are considered important to the veterans (and some could certainly turn out to be stronger risk factors than Agent Orange), then the base population should be expanded to include older men, thereby increasing the number of cases and the power of the study considerably.

Finally, I would like to congratulate the authors on their superb work, and to thank Howard Ory for providing me with the opportunity to review the protocols. It has been my pleasure and to my benefit to have done so.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date July 1, 1983

From Chief, Respiratory and Special Pathogens Epidemiology Branch
Division of Bacterial Diseases, Center for Infectious Diseases

Subject Proposed Agent Orange Study

To TO THE RECORD

The general outlines of the study proposed by CDC to study the health effects of Agent Orange in particular, and the Viet Nam experience in general are a reasonable approach to the problem. Of necessity, many details remained undefined at this stage of protocol development so that a specific critique cannot be made. Many of the concerns which might be raised are already mentioned in the protocol and resolution of these issues will await the results of the pretest. However, it may be worth emphasizing some of the concerns already raised by the proposal as well as indicating some other areas where further clarification might be useful.

One of the major difficulties with the study is the potential for accurate assessment of exposure to Agent Orange. Although the authors have indicated their approaches to the problem in considerable detail, I was concerned at the lack of assessment of the validity of military records or any other attempt at independent assessment of exposure. Will the Ranch Hand studies address the issues of how closely herbicide distribution runs actually complied with flight plans? The three scoring systems proposed provide flexibility in weighting recent heavy exposures versus "low level" exposures. However, it may be helpful to look in more detail at the actual profiles of exposure in terms of whether it may be possible to define populations of intensively exposed troops versus populations with more extensive low level exposure. This type of exposure differentiation might be masked by the use of the scoring systems. Finally, if it develops that the exposure information available from military records will be inadequate to differentiate between the most likely exposed and the least likely exposed in the area with heavy Agent Orange useage, consideration should be given to changing the sample size calculations, since misclassification bias could be substantial.

An additional problem with the exposure measure is the sample size calculation for the case control study of soft tissue sarcoma. The power is calculated on the basis of 10-15% of the control population being Viet Nam veterans, but I do not see any estimate of the proportion of Viet Nam veterans who are likely to have been exposed to Agent Orange. Since the hypothesized increased relative risk would be presumeably in comparison to the proportion of the controls who had actually been exposed to the risk factor, sample size calculations should take that into account. An estimate of the proportion actually exposed to herbicides may be difficult to come by, but at least a crude estimate should be attempted and the implications for power should be considered. It is possible that this would have implications for more active recruitment of other population based cancer registries or for extending the projected period of the study.

JUL 6 1983

In terms of outcome measurements, many of the potential outcomes will of necessity be subjective; however, all efforts should be made to obtain objective documentation of outcome. For example, detailed information on employment history, and lack of employment; hospitalization, particularly including psychiatric hospitalization; and arrest records, might be useful adjuncts to the study. Furthermore, I think more specific mention should be made of plans to obtain both previous and subsequent medical records for documentation of abnormalities reported in the history and physical examination phase. Similarily, the literature review suggested that nerve conduction velocity studies had been useful in some of the background studies. I think it would be appropriate to either indicate why this tool was not appropriate for inclusion in this study, or whether plans would be made for testing a subset of the population. I thought the protocol did not deal adequately with the difficult problem of findings which might either constitute confounders or outcome variables in themselves such as certain sociopsychological difficulties.

I thought more scepticism should have been expressed about the potential difficulties when dealing with the variable, illicit drug use. Although use of controls may help in dealing with this potential confounder, it is conceivable that use of drugs (with resultant health effects) and subjective experience of exposure to Agent Orange, may be related.

It may be helpful to emphasize more strongly that subjective symptoms may or may not result in data which can be usefully analyzed.

Claire V. Broome, M.D.