Item ID Number	01720
Author	
Corporate Author	Office of Technology Assessment
Report/Article Title	Typescript: Office of Technology Assessment Review of Centers for Disease Control Protocols for Epidemiologic Studies of the Health of Vietnam Veterans, July 1983
Journal/Book Title	
Year	0000
Month/Day	
Color	☐
Number of Images	45
Description Notes	

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 Staff

H. David Banta, Assistant Director, OTA

Clyde J. Behney, Health Program Manager

Michael Gough, Project Director
Hellen Gelband, Analyst
Robert Berenson, Consultant

Virginia Cwalina, Administrative Assistant
Jennifer Nelson, Secretary
Mary E. Walls, Secretary

Office of Technology Assessment

AGENT ORANGE STUDY PROTOCOL REVIEW
Advisory Panel

Richard Remington, Ph.D., Chairman
Vice President for Academic Affairs
University of Iowa
Iowa City, IA 52240

Margit Bleecker, M.D.
The Johns Hopkins Medical Institutes
School of Hygiene and Public Health
Division of Occupational Medicine
615 North Wolfe Street
Baltimore, MD 21205

George L. Carlo, Ph.D.
Epidemiology, Health &
Environmental Sciences
1803 Building
Dow Chemical U.S.A.
Midland, MI 48640

Neal Castagnoli, Jr., Ph.D.
Department of Chemistry &
Pharmaceutical Chemistry
University of California
San Francisco, CA 94143

Theodore Colton, Ph.D.
Boston University School
of Public Health
800 East Concord Street
Boston, Massachusetts 02118

Mr. Frederic Halbert
12150 Banfield Road
Delton, MI 49046

George B. Hutchison, M.D.
Harvard University School
of Public Health
677 Huntington Avenue
Boston, MA 02115

Patricia King, Esq.
Georgetown Law Center
600 New Jersey Avenue, N.W.
Washington, DC 20001

Lewis Kuller, M.D.
Dept. of Epidemiology
Graduate School of Public Health
University of Pittsburgh
130 DeSoto Street
Pittsburgh, PA 15261

Claire O. Leonard, M.D.
1445 Wilton Way
Salt Lake City, Utah 84108

John F. Sommer, Jr.
The American Legion
1608 K Street, N.W.
Washington, D.C. 20006

Mr. Theodore P. Sypko
Veterans of Foreign Wars of
the United States
V.F.W. Memorial Building
200 Maryland Avenue, N.E.
Washington, D.C. 20002

Mr. John F. Terzano
Vietnam Veterans of America
329 Eighth Street, N.E.
Washington, D.C. 20002

Mr. Monte C. Throdahl
Sr. Vice President, Environmental
Policy Staff
Monsanto Company
800 N. Lindbergh Blvd.
St. Louis, MO 63166

H. Michael D. Utidjian, M.D.
Corporate Medical Director
American Cyanamid Company
Wayne, NJ 07470

December 1982

Table of Contents

Table of Contents (continued)

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.

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 sarcoms.

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	3.2	590 (18.3)
	32,251 (100)	8241	2654	8.2*	3217 (100)

*Percentage Vietnam era veterans in U.S. male population ages 30-49: $\frac{2654}{32,251} = .082 \times 100 = 8.2\%$

[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 game 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 "soldiering 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 be undertaken for other than scientific 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 sufficiently 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 chloracmure 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 no other source 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 physical 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 Protocol:

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

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.

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