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PROTOCOL

for

Epidemiologic Studies of Agent Orange

Submitted January 22, 1982

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I. Introduction

Many technical military and scientific terms and abbreviations are used throughout this text. Please see the glossary (Appendix A) for definitions, if necessary.

The major portion of the Vietnam war for American troops was between the years 1965-1972. American troops had been in Vietnam prior to 1965, although their numbers were small. From 1965 the number of U.S. troops grew rapidly to a peak in 1968. During that year there were estimated to have been over a million men present in Vietnam.

The Vietnam era, by Presidential Proclamation, officially dates from August 5, 1964, to May 7, 1975. In this time period an estimated 9 million men served in the U.S. Armed Forces. Of these, approximately 2.2 to 2.8 million served in Vietnam; 1.6 million saw action in combat; 309,000 were wounded in battle; 47,000 died as a result of acts of war.

Defoliants were used in South Vietnam from January, 1962, to February, 1971, mainly to deprive the enemy of cover. They were also used, to a much lesser degree, for crop destruction in areas of heavy Viet Cong activity and to maintain a clear perimeter around some base camps. Herbicides Green, Pink, and Purple contained about 40% of the estimated 368 pounds of 2,3,7,8 Tetrachlorodibenzo-p-dioxin (TCDD) dropped in Vietnam. However, the use of these herbicides is not considered to be

a relevant concern because they were sprayed in limited quantities on less than 90,000 acres primarily from 1962 to 1964, a time when few U.S. servicemen were in Vietnam. In contrast, 90% of Agent Orange was used on over 2.9 million acres during a time when large numbers of U.S. troops were in Vietnam, early 1965 to April 1970. Agent Orange is an approximate 50:50 mixture of the herbicides 2,4, dichlorophenoxy acetic acid (2,4-D) and 2,4,5 trichlorophenoxy acetic acid (2,4,5-T). This latter substance was contaminated with varying amounts of TCDD. A brief summary of the use of the defoliants is included in Appendix A. The interested reader is referred to excellent summaries presented in the 1974 National Academy of Science report (1), the Air Force document prepared by Major Alvin Young (2), and the new VA sponsored literature review (3).

The work represented in this protocol was conducted under contract to the Veterans Administration. We were charged with developing the protocol for an epidemiologic study of ground troops exposed to Agent Orange while serving in South Vietnam. To complete this charge we: held extensive discussions with Army records personnel; reviewed selected Army and Marine Corps records; investigated Army historical materials; reviewed literature on Agent Orange, its constituents, its environmental behavior and its human and animal effects; reviewed the popular press, television documentaries, congressional testimony and other

non-scientific sources of information; consulted with the Air Force and Australian investigators about their studies; and followed-up many leads on other possible sources of data and information relevant to this study.

The initial draft, which emphasized preliminary studies rather than details of the recommended historical cohort study, has been reviewed by three review groups. On the basis of detailed comments from these groups we have revised the protocol. The original draft section III on epidemiologic studies has been moved to Appendix B.

This protocol draft is organized as follows:

In section II (Background) we provide a brief review of information relevant to the design of this epidemiologic study including: the environmental fate of the constituents of Agent Orange, the animal and human health effects literature, a review of the popular press, and a brief summary of several current approaches to studies of Agent Orange, both epidemiologic and non-epidemiologic. Details of the background section are presented in separate appendices.

In section III we present a detailed protocol for the historical cohort study which provides the detail necessary for an epidemiologic study team to organize and conduct a pilot study of the protocol. This protocol incorporates many of the suggestions made by reviewers of the first draft protocol. We believe a pilot study to be

mandatory to adequately test the feasibility of conducting the full study, to fully develop all study procedures and data collection forms and to estimate study costs.

We originally proposed a series of studies utilizing death certificates. We have not included these studies in this draft. We recommend that the VA complete a proportionate mortality analysis, and a frequency distribution of all complaints in the Agent Orange Registry, as rapidly as possible so that the information can be incorporated into the final design of data collection instruments for this study.

II. Background

A. Environmental Toxicology

A detailed literature review and discussions of this topic is included as Appendix C and summarized here.

Herbicides were used in South Vietnam between 1962 and 1971 with the majority of use after 1965. Several different compounds were used including 2,4 Dichlorophenoxy acetic acid (2,4-D), 2,4,5 Trichlorophenoxy acetic acid (2,4,5-T), picloram and cacodylic acid. Agent Orange was the name given to an approximately 50:50 mixture of 2,4-D and 2,4,5-T. The 2,4,5-T component was contaminated with 2,3,7,8 Tetrachlorodibenzo-p-dioxin (TCDD), at a level of 0.02 to 47 (average about 2) parts per million.

The two herbicides in Agent Orange (2,4-D and 2,4,5-T) have relatively short half-lives in soil (up to 3 weeks) with little soil penetration. The degradation is apparently even faster in tropical soils. TCDD may be persistent in soil but the persistence seems to be limited to areas where massive application has occurred.

TCDD when present in soil appears to be stable with exceedingly low levels present in water runoff. When present in water systems, TCDD appears to be bound to sediments. The 2,4-D and 2,4,5-T are more likely to contaminate runoff water. Photodegradation of all three compounds is well documented. Under conditions present in Vietnam, TCDD photodegradation is measured in hours.

Degradation of 2,4-D, 2,4,5-T and, to a lesser degree, TCDD is enhanced by microbial action. TCDD appears not to be volatilized.

The environmental fate of the three constituents of Agent Orange are not fully understood. Even though rapid degradation appears most likely, it may be necessary to devise exposure indices for this study based on several assumptions. At a minimum these would be to assume rapid degradation for one index and long term persistence for another. The use of several assumptions would increase the likelihood of detecting an Agent Orange effect if there is one.

Picloram and cacodylic acid do not appear to be sufficiently toxic to be of major concern. However, it may be possible to incorporate some investigation of these agents into the study as well.

B. Animal Studies

The components of Agent Orange have been studied extensively in a wide variety of animal species in the laboratory and in the field. A review of selected articles is presented in Appendix D and is summarized here.

The dioxin contaminant (2,3,7,8-TCDD) has received considerable attention in the literature and is thought to be the most toxic synthetic chemical known. It is toxic in at least one organ system in every animal species tested. Additionally every organ system has been affected in at

least one animal species. Among the major effects in animals are: high fatality (low LD50) in many animals, liver toxicity, effects on the lymphatic system and immune response and teratogenicity. Carcinogenic effects have been reported in some species. Thus far, no evidence has been reported for transmittal of genetic effects from an exposed male to its offspring although this area has not been extensively studied. The teratogenic studies have typically used massive doses, unlikely to be encountered in human exposures, and the teratogenic effect has not been found in some species. (See Appendix E for a summary/discussion of the literature on reproductive effects.)

While toxic effects have been reported in many different species, the severity of the effects, the dose required to produce the effect, the LD 50 and the metabolism and storage of the dioxin vary widely. Thus, extrapolation to humans should be done with extreme caution.

The other two components of Agent Orange have been found to be only moderately toxic in animals. Reported effects have included teratogenesis, nervous system abnormalities and carcinogenesis but the literature is not conclusive and the required doses were generally quite large.

C. Human Health Effects

Information on the human effects of the constituents of Agent Orange (2,4-D; 2,4,5-T and its contaminant

2,3,7,8-TCDD) has come from studies of occupational exposures, occupational accidents, poisonings and general population exposures. Many involve fairly high dose exposures in small populations, and few are properly conducted epidemiologic studies. A selective literature review and discussion is presented in Appendix F and summarized here.

The least hazardous of the substances is 2,4-D. Common symptoms following acute exposure to high doses include headache, weakness and gastrointestinal upset. Central nervous system dysfunction, peripheral neuropathy, nephropathy and asthenia have also been reported. Apparently, 2,4-D is not contaminated with 2,3,7,8-TCDD. The potential exposures to 2,4-D among the ground troops in Vietnam were not likely to be high enough to be of concern.

Since 2,4,5-T is contaminated with 2,3,7,8-TCDD, these substances have been largely studied together. The 2,3,7,8-TCDD contaminant appears to be the more toxic of the two (2,4,5-T appears to have only moderate toxicity) in animals, but the toxicity in man is uncertain. Chloracne is the only established health outcome associated with dioxin exposure. It is not an adequate marker of dioxin exposure, however, since it is difficult to diagnose, occurs after exposures to other chemicals and does not always appear even after heavy dioxin exposure. A number of other health effects have been reported affecting every organ system of

the body. These include porphyria cutanea tarda, other skin disorders, liver damage, disorders of lipid and carbohydrate metabolism, peripheral neuropathy, central nervous system dysfunction, teratogenesis, cancer and psychiatric disorders. The evidence is not clear for any of these.

The literature on reproductive effects (see Appendix E) does not support any effect at this time. If the exposure were having a teratogenic effect, it could be expected to produce a common syndrome as is characteristic of other teratogens. An effect through the male, however, is most likely to be a mutational effect. Dominant mutations occur spontaneously and increase with age, thus making study difficult. Recessive mutations would not be demonstrable in the offspring of the exposed male, and would only be demonstrable in later generations with enormous numbers of study subjects.

While the scientific literature does not provide a unequivocal focus for a study of effects of exposure to Agent Orange, it does suggest many types of effects which should be examined. These suggested effects are addressed by the protocol.

D. Popular Press

Because this study has been mandated to address a highly emotional and political situation as well as to answer an epidemiologic question, nonscientific as well as scientific issues must be considered. The popular press has

been selectively reviewed to gain an understanding of the nonscientific issues important in designing a study which is acceptable to veterans and the public and is scientifically sound. A detailed review is presented in Appendix G and a summary is presented here.

Much information on the use of Agent Orange in Vietnam has been presented, but with conflicting details. Confusion is likely to exist in the minds of veterans and the public on this subject. Veterans have been informed that those at highest risk of exposure are those who may have had direct contact with the herbicide: Operation Ranch Hand personnel; Ranch Hand ground support personnel; drum handlers; backpack sprayers; door gunners for spray helicopters; service helicopter units; and combat engineers. About 50 symptoms/diseases which veterans attribute to Agent Orange exposure have been reported.

The nonscientific media have highlighted several factors which might complicate a study of health effects among Agent Orange exposed ground troops. Veterans and the general public are likely to be aware of and expect to see the following issues addressed in our study design: possible sources of 2,4,5-T and dioxin exposure other than the use of Agent Orange in Vietnam; other exposures which might be associated with outcomes similar to those veterans are attributing to Agent Orange (e.g., the total "Vietnam experience", the use of other herbicides, the spraying of

insecticides in Vietnam, wide use of illicit drugs among U.S. troops); suspected VA bias against finding Agent Orange related problems; difficulty of using existing records to determine the exposure of ground troops to Agent Orange; and the proposed "time-bomb" mechanism by which delayed effects of Agent Orange are experienced following weight loss.

It will be difficult to control for possible U.S. sources of exposure to dioxins. Some control of the problem may be possible through analytic techniques such as stratification on urban/rural residence and geographic region of residence. The problems of other Vietnam exposures (confounding factors) and the suspected VA bias are dealt with in the protocol (section III). The possibility of the "time-bomb" mechanism can only be evaluated through long term follow-up of the veterans selected for study. However, biologically this seems an improbable mechanism since the men during their Vietnam service would be likely to have been at their leanest. The major portion of their stored fat is most likely to have been added since the time of exposure, and major weight loss is most likely to be a sign of disease rather than a cause.

E. Studies of Agent Orange by Other Investigators

The focus on Agent Orange in the past five years has resulted in a number of different studies among Vietnam veterans, some completed and some ongoing. Many of

these we have classified as non-epidemiologic since they consist of the uncontrolled collection of data from volunteers. They may, nonetheless, provide useful information. We summarize below some of the non-epidemiologic studies and the current epidemiologic studies which have come to our attention.

1. Non-epidemiologic

Several studies have been undertaken by veterans groups and by the Veterans Administration to gather data on the health effects that could be related to Agent Orange exposure. Participants have, for the most part, been volunteers. Thus any results obtained are likely to be biased in the direction of over-reporting of conditions linked to a presumed exposure to Agent Orange. In addition, no control group (i.e., veterans not exposed) is available for comparison. (All of these studies could be considered case series.) Despite the problems, these studies may have value in identifying types of conditions that should be looked for in a controlled study of the effects of Agent Orange.

The first of these ad hoc studies was done in 1977 by Maude de Victor a VA claims worker in Chicago. She processed a claim, made by a veteran who was dying of lung cancer, that his illness was due to "those chemicals" in Vietnam. She identified 35 other Vietnam veteran patients who she felt could be suffering from dioxin poisoning. Her

findings were publicized through a Chicago TV station (Uhl and Ensign, 1980, pp. 193-195).

Following the interest developed from de Victor's results, Citizen Soldier, a G.I. and veterans rights organization based in New York City, offered a toll free phone service to veterans who had concerns about Agent Orange exposure. Callers to this "hot line" numbered about 3,000 by the end of the summer in 1978. Each was sent a six page self-administered medical questionnaire that had detailed questions in the areas of military-service history, perceived herbicide exposure, personal health history, past medical history, and family history, with an emphasis on stillbirths, miscarriages, and congenital birth defects. By November, 1,000 questionnaires were returned and 536 were coded. Reported cases of cancer and birth defects were verified with local physicians or medical records. From the results of this select group of responses 35 cases of cancer were reported (included 3 cases of kidney cancer, 3 of testicular cancer and a number of lymphatic system cancers); 77 children were reported to have been born with defects; and large numbers of respondents complained of changes in skin color, sensitivity to light, and nervous system difficulties (Uhl and Ensign, 1980, pp 197-209).

Other "hot line" programs have also been established and have resulted in reports on the health effects of Agent Orange. For example in September, 1980, the Vietnam

Veterans of America announced the development of a hot line to provide vets with information. The callers were sent a medical questionnaire that was to be evaluated by faculty members at Columbia's School of Public Health. (Muller, 1981, pp.32-33). We have not found any report of this analysis. Another veterans group in St. Louis, Missouri, called CAVEAT (Concerned American Veterans Against Toxins) conducted extensive phone interviews with veterans and others (eg., highway crew members) concerned about exposure to herbicides and provided a listing of reported symptoms obtained including numbness, nervous disorders, psychological effects, skin rashes, alterations of the sex drive, cancer, and birth defects (Furst, 1981, pp.39).

The Veterans Administration has also initiated the development of a data base called the Agent Orange Registry to record information on veterans who are concerned about possible health effects resulting from exposure to herbicides in Vietnam. Information obtained is derived from a questionnaire, physical examination and a set of laboratory tests. As of October, 1981, 51,658 veterans had been examined and their data computerized. A Data Analysis Task Force has been established to evaluate the information obtained.

2) Epidemiologic

The Air Force has designed and is now in early stages of implementation of a study of the aircraft

crews who were involved in Operation Ranch Hand. This was the name given to the defoliant spraying operation in South Vietnam. The Air Force study is a historical cohort design (see Appendix B for a discussion of this design)in which the study group consists of all C123 crew members involved in the Ranch Hand Operation. A control group of larger size will be constructed utilizing similar Air Force personnel who were not involved in the spraying program. Each of the study and control members will be examined according to an extensive protocol involving physical examination procedures, laboratory and questionnaire. The protocol calls for long-term follow-up and regular re-examination of both groups. Preliminary results of the Ranch Hand study should be available in time to assist in early phases of a ground troop study.

The Ranch Hand study presents a situation distinctly different from that confronted in a study of ground troops. The Ranch Hand cohort is a well-defined group of limited size, with known very heavy exposure to Agent Orange. Thus, the conduct of a historical cohort study in this group is relatively straightforward. The study has been criticized on the basis of small sample size. While it is true that the sample size, (approximately 1200 exposed) is relatively small, the criticism is only partially warranted. When faced with a limited population of this type, in which there is no possibility of an increase in sample size, the

epidemiologist must make the best possible use of the limited population. Care must be taken of the obvious limitations in the results concerning rare disease, but the population should be fully utilized for the important information which can be obtained on more common diseases from a group with heavy exposure.

The Australian government is currently in the planning stages of a study of Australian ground troops potentially exposed to Agent Orange in a fashion similar to the American troops. Currently the focus is on development of a historical cohort study in which the study group would be defined on probability of exposure to Agent Orange. They are considering a control group of non-Vietnam veterans. The Australian group is currently working on a feasibility test of the exposure gradient construction and is considering a variety of preliminary studies of a case-control nature (see Appendix B for definition and uses of this design). Results from the Australian preliminary and pilot studies should be available in time to assist in planning of the U.S. ground troop study. Since the Australians are also studying ground troop exposures, the U.S. and Australian studies should be closely coordinated.

The Center for Disease Control is now conducting a case-control study of birth defects. The cases will be birth defects drawn from the metropolitan Atlanta birth defects registry. The cases will be matched with normal

births in the same area. The case and control fathers will be compared as to Vietnam service experience. Early results of this study may be available in time to assist the ground troop study.

Several state health departments are either planning or conducting studies of their own veterans. The State of Michigan particularly has conducted a mailed questionnaire survey of its veterans and is pursuing some additional data gathering. The results of this work should be of help in further design of the ground troop study.

III. Proposed Protocol

A. Introduction

In the following sections we detail the protocol for the proposed historical cohort study. These details include a full questionnaire, details of the proposed exposure likelihood index and the complete physical exam protocol. We feel that these materials should be released only to scientific review groups. Knowledge by veterans of their presumptive exposure (according to the study) and of the details of the examination instruments would probably make a valid epidemiologic study virtually impossible.

The planning of an epidemiologic study is usually a lengthy process. The process in the current study is much more complex than usual. The large size of the potential population involved (2.5 million men estimated), the large and varied geographic region in which military activity took place, the complexity of the military operations, the variety of potentially confounding exposures (such as combat experience itself, possible exposure to malathion, other defoliants, chloroquine, Dapsone, illicit drugs and riot control agents) along with the lack of detailed data on exposure to Agent Orange all make the problem of defining and sorting out the specific effects of Agent Orange exposure much more complex. In addition, in order to use the military records and to understand the variety of confounding factors which must be taken into account to

construct a study and control group requires that the contractor become relatively expert in military terminology and operations. The extreme interest of the public in this study imposes a greater than usual need for additional planning of safeguards against bias which are beyond those normally required in an epidemiologic study.

The Air Force has spent more than 3 years developing the protocol for their study which is a more straightforward research problem than that of a ground troop study. The Australian group planning their study of Australian Vietnam veterans has been working for almost two years and is currently proposing cohort construction testing and preliminary studies to gather additional relevant data completing a design for a full historical cohort study. Thus it is clear that more than several months will be required to complete this study.

B. Methods

1. Summary of study design

The recommended study uses an historical cohort design comparing presumed highly and minimally exposed cohorts for health outcome. The study cohorts should be defined through the use of Army and perhaps Marine Corps records for the period 1965-1971. The most feasible plan is to select high and low likelihood of exposure groups which have maximal possible separation of exposure probability. Battle casualties should not be included in the cohorts, nor should re-enlistees, officers or other with multiple Vietnam tours, unless an easy method of selecting comparable cohorts of officers and multiple tour of duty personnel can be devised. Existing records of both the active duty and veteran periods should be abstracted for each member of the cohorts. All members should be traced as necessary to determine current vital status, and be examined by a standard protocol including an extensive questionnaire, physical examination and laboratory testing with input from current and past physicians.. Data analysis should address the quality of the data collected and the comparability of the cohorts as well as the association between exposure status and health status.

2. Rationale for historical cohort study

In many epidemiologic studies of the possible health effects of environmental exposure, the

anticipated outcomes associated with even high levels of exposure may be very poorly defined, very diffuse or otherwise difficult to predict in advance of the study. These problems of defining the possible outcomes may be due to 1) an incomplete understanding (if any) of the effects of the chemical constituents of the exposure on humans, 2) a possible effect on multiple systems which can result in a number of widely differing observed outcomes among affected persons and 3) the tendency of persons who believe themselves to have been exposed to attribute all their particular health problems to the exposure, offering the investigator a wide variety of complaints of exposure effects with which to deal.

For Agent Orange, a great deal of animal work has been done on the subject of 2,4-D, 2,4,5-T, and TCDD exposure. These results of animal studies are not consistent. Effects have been observed in all organ systems but with much variation from one species to another in the range of observed effects and in the dose required to produce an effect.

The knowledge of human health effects is much less complete than that of animal studies and is more contradictory. We have compiled a list (see Appendix F) from the literature of more than 100 suspected symptoms or diseases potentially associated with exposure to Agent Orange. Thus, there is as yet no firm disease outcome

established in any human population which could be used for developing a case-control study of the effects of exposure to Agent Orange in Vietnam veterans.

Because the outcome is difficult if not impossible to define, the case-control approach, dependent on the clear identification of an outcome cannot be used. In the absence of a well defined outcome, a cohort study design is required. Since exposures took place 10-15 years ago and since a rapid answer to the question of adverse health effects from Agent Orange exposure is desired, the historical form of the cohort study, in which persons are identified from past records in terms of their exposure and followed for outcome status over time, is required. In this case, it may be possible to identify exposures occurring ten to fifteen years ago, and thus to start the post exposure follow-up at the point of probable exposure. This would allow 10-15 years of observation of health and disease in exposed and unexposed veterans. For certain outcomes, such as cancer, it could be necessary to follow the cohort into the future, 25-35 years post exposure, because of both the induction or latent period for the various cancers and because the exposed veterans will, on the average, only then have reached the age of most frequent diagnosis of cancer.

3. Development of Exposure Likelihood Index

Limitations

The most critical step in establishing an historical cohort study of Agent Orange is to estimate the exposure to Agent Orange with sufficient detail and accuracy to allow the identification of two or more groups with a meaningful difference in exposure. Unfortunately we have identified no mechanism which would allow precise documentation of actual exposure. We recommend, therefore, the development of an exposure <u>likelihood</u> index. This index, if properly constructed, should allow separation of individuals along a gradient of their probability of having been exposed to Agent Orange in Vietnam. The development of this exposure likelihood index is beyond the scope of our current contract because of 1) the volume of records which must be reviewed, 2) the disorganized state of the records and 3) the necessity for hand review and abstraction of all records by persons with appropriate security clearances.

Unfortunately, the need for eventual systematic review of spraying records was not anticipated during the Vietnam conflict. Thus, the records are found in varying types of forms and in varying degrees of completeness without any organized listing of data sources. Therefore, we can at this time only outline below the general approach which should be taken to develop this index from the records

currently known to be available.

Summary of Procedure

The development of the exposure likelihood index should follow six steps. These steps are:

Step 1: Document Agent Orange use (including Ranch Hand, helicopter spraying, surface spraying, aborted missions, military occupational exposures and accidents) by location, date and quantity used per unit area.

Step 2: Identify company headquarters in high and low use areas.

Step 3: Integrate data on Agent Orange use and troop location to develop likelihood of exposure indices for individual companies for short time intervals (day-by-day if possible). This likelihood of exposure index should be based primarily on frequency of exposures although consideration should be given to differentiating between exposure to aerial spraying which is probably lower dose and other exposures such as hand spraying and being under abort mission drops which were probably higher dose exposures.

Step 4: Identify soldiers in companies by dates present

Step 5: Using the likelihood of exposure daily indices for the companies in which the soldiers identified in step 4 served, develop a cummulative individual likelihood of exposure for each soldier by summing the number of exposures he encountered.

Step 6: Order troops by individual cumulative likelihood of exposure levels into a spectrum from high to low. Select members of the high and low likelihood of exposure cohorts from the extremes of the spectrum. The exact cutoff levels, whether in percentiles or frequencies of exposure will have to be set when the number of troops and breadth of the spectrum of exposure are known. The cut offs should be set to maximize the differences in exposure between the two cohorts.

We have received a copy of the December 1981 proposal, "Proposed Agent Orange Troop Exposure and Non-Exposure Cohort Selection concept Paper" by Dr. Bricker of the Department of Defense (DOD) (included as Appendix H). The approach outlined by Dr. Bricker is in basic agreement with our own. The major difference is that we propose that the presumed exposure likelihood level be verified for each individual soldier by establishing the company(ies) and dates of service. This procedure would allow for turnover, R and R leaves, hospitalizations and temporary duty

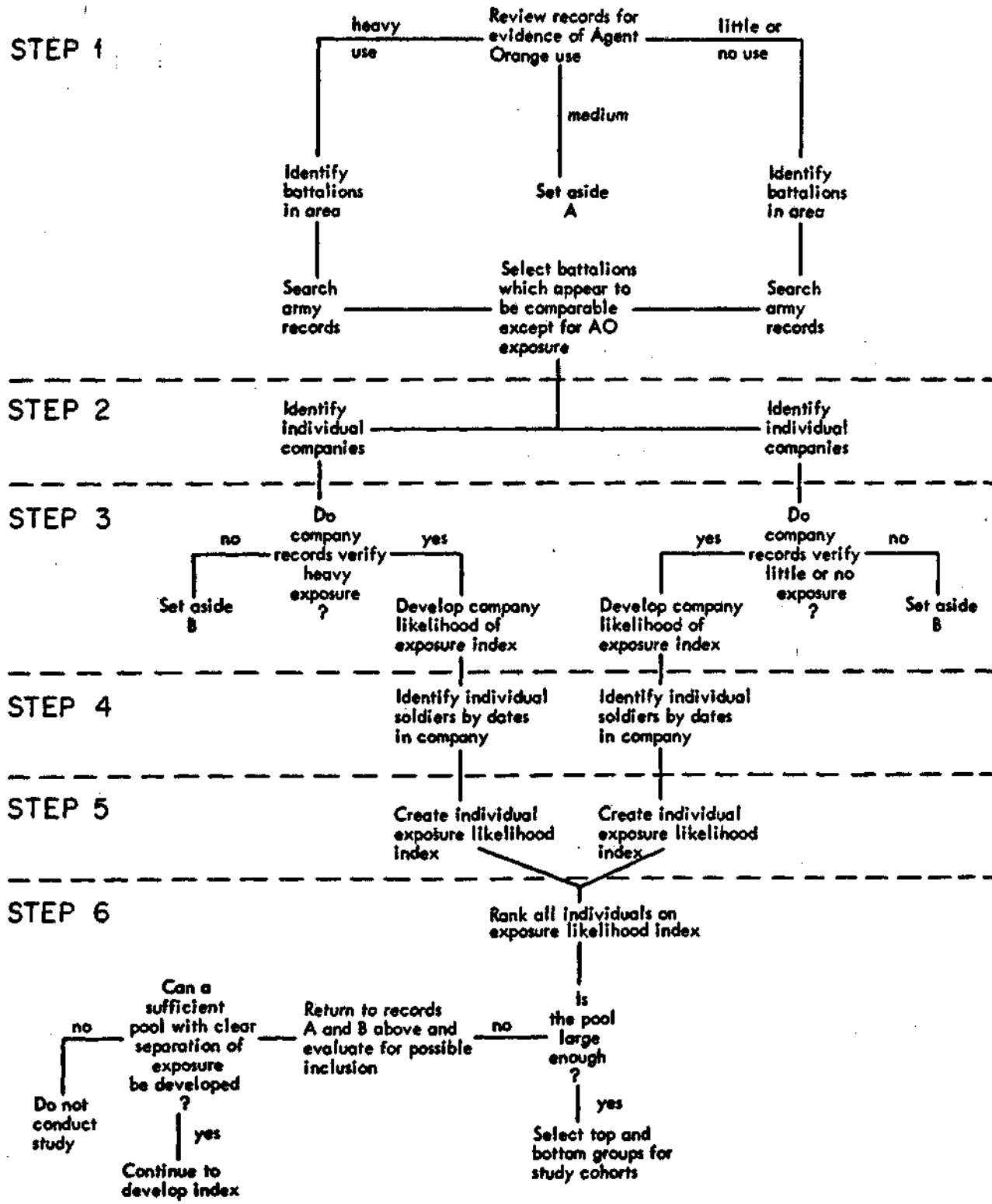
assignments all of which can introduce serious problems of misclassification into an index based only on company data. The individual index is also necessary to verify non-exposure for the low likelihood cohort.

A flow chart illustrating these steps is given in Figure 1 and details are discussed further below.

1) Documentation of Agent Orange Use

The first step in the development of the exposure likelihood index should be the collection of all available data on the actual use of Agent Orange in South Vietnam. This has, of course, been done for the Air Force spraying missions which are recorded on the HERBS tape. However, Agent Orange was also used at times in helicopter missions, riverine operations, roadside spraying operations and basecamp perimeter spraying, and probably in other ways as well. In addition, Secretary Schweiker on September 23, 1981, announced that there were records of 92 aborted Ranch Hand missions in which the load of Agent Orange was rapidly dumped for safety reasons to lighten the load on the aircraft. There are now known to have been over 180 such aborted missions. There appear to have been four bases where aborted missions potentially exposed a total of over 25,000 men. There have also been reports of several major accidents involving leakage of Agent Orange from storage facilities. Any of these situations could potentially have

Fig. 1 FLOW CHART OF DEVELOPMENT OF EXPOSURE LIKELIHOOD INDEX



exposed groundtroops to Agent Orange. Unfortunately, records of such activities were not kept in any organized fashion and may be difficult to verify.

A complete search of all Army records would be quite costly. We recommend as a minimum that the Military Assistance Command Vietnam (MACV) records be reviewed in detail for evidence of Agent Orange use and to establish geographic areas and time periods of most frequent and least frequent use (hopefully zero use). The review of lower command level records for Agent Orange use could be postponed until tentative selection of likely candidate battalions is made so that review could be concentrated on these. The battalions which were operating in areas known to be heavily sprayed through Ranch Hand records and/or who have been associated with possible heavy exposure from other types of records should be selected for screening of companies and platoons for which exposure likelihoods should be developed. Likewise, battalions which appear to be largely free of these possible exposures should also be selected for screening of companies and platoons for which exposure likelihoods (which are expected to be low) should be developed. Concentrating efforts on these 2 types of battalions would have the best probability of success and keep the cost of the record review down.

In all cases of identified use of Agent Orange, the locations must be recorded as precisely as possible in the UTM (Universal Transverse Mercator) system by calendar date and time. In addition, if possible, the magnitude of use should also be recorded.

2) Troop Movements

In order to develop the exposure likelihood index a thorough review of troop locations which can be correlated to areas of exposure must be made. The troop locations should be identified at the company level, or platoon level if possible. While the location of the company headquarters is certainly not as precise an estimate of the location of a given soldier as that soldier's actual location on a given day, the company headquarters is the most precise locational information which is consistently available. There are no consistent records which can identify the location of individual soldiers reliably. The placement of an individual in the proximity of his company headquarters provides better precision than placing him at the location of the battalion headquarters. According to DOD personnel with whom we have discussed this problem, combat units, at least, would locate company headquarters in a relatively stable position over a period of several weeks. The troops would then operate in a relatively confined area around the headquarters location. It should be possible to locate the

company headquarters through the use of the battalion S3 (operations officer) records. These should be supplemented for greater accuracy by the use of a variety of other records including: the Operational Report Lessons Learned and the After-Action Reports, both of which relate to special operations activities; the Brigade Situation Reports and Daily Journals; the company Morning Reports and the Organizational Histories. In addition to combat units, other potentially useful groups, such as special forces units, chemical detachments and engineering units, should also be thoroughly investigated. The investigation of these other units may require the review of different types of records.

3) Company Likelihood of Exposure

The third step in the development of the exposure likelihood index would be to relate steps one and two in order to construct a company level likelihood of exposure index. This index should be constructed for as small a time unit as possible, preferably on a day-by-day basis. There are a variety of potential ways in which this company level exposure likelihood index could be constructed. One possibility would be to divide the area of South Vietnam into grids of a standard arbitrarily defined size such as squares of 10 km on a side. Every use of Agent Orange within a grid for a given time period, such as one month,

could be tabulated and the number of such uses assumed as an arbitrary level of exposure. The placement of a company within that grid in the same time period could then be assumed to represent an exposure of all individuals in the company at that time to that level of Agent Orange. This system, while perhaps relatively easy and unambiguous in its construction; 1) would assume that Agent Orange persisted in the environment, 2) would assume that location in the grid prior to actual spraying would constitute an exposure, 3) would assume that the average exposure over the interval was that of the highest exposure tabulated during that interval and 4) would lead to a certain level of misclassification, depending on the vagaries of spray location and troop locations in relation to the arbitrary division of the grids.

A second method of relating Agent Orange use and troop locations would be to utilize a computer program to compare the day-by-day locations of Agent Orange use to the day-by-day locations of company headquarters, utilizing an arbitrary set of criteria for both time and distance proximity as the definition of a "hit". For instance, for the fixed wing spraying, the proximity definition could be, location of company headquarters simultaneously within one kilometer and within a two day period of time following the use of Agent Orange.

As an alternative, although complex and more costly, such a procedure could be performed by utilizing actual distances and time following exposure in an algorhithm which would have a decreasing probability of exposure according to both increasing distance and time following the Agent Orange application. This technique, however, implies greater accuracy than is probably warranted.

Another possible refinement to such a mechanism for developing the exposure likelihood index would be to utilize an arbitrary weighting scheme in which a second application of the herbicide within a defined period of time, such as between four and twelve weeks following the first application, would be assumed to have a greater exposure potential than the first application because of partial defoliation, particularly of the highest canopy as a result of the first application. The arbitrary weighting could be applied to produce a higher index for troop exposure in proximity to a second spraying than to a first spraying.

4) Identification of Individuals in Companies

The fourth step in the development of the exposure likelihood index would be to place individuals within the company on a day-by-day basis. The primary document for this step is the company level Morning Report. These reports show, for any given date, significant events relating to individuals including transfers in and out of the company, temporary duty assignments and R and R assignments. All of these assist in placing an individual at the company level on a given day. In order to fully define the presence or absence of all individuals in a given company for a specified short time period such as one week, the Morning Reports for that company would have to be reviewed for up to six months preceding and following the specified time period to identify all material relevant to a given individual. This is the result of the fact that company commanders frequently did not learn of medical evacuations or other reasons for absence until months later, and that personnel orders were often changed after issuance to the company. The review of the Morning Reports should be supplemented by the use of a variety of other records, such as Personnel Type Order Files, Special Orders, Line of Duty Files, Welfare Fund Files, and possibly some other files which must be investigated for content such as Command Reporting Files and General Finance and Fiscal Files.

5) Individual Exposure Likelihood Index

After completion of the roster of individuals in a given company and the dates of presence in the company for each individual, the fifth step in development of the exposure likelihood index would be to relate this file to the company day-by-day exposure index. A cumulative exposure likelihood index can be built for each individual by summing the number of times he was actually present in a company at a time the company was potentially exposed taking into account transfers to other companies, leaves etc.

6) Construction of an Exposure Likelihood Gradient

Once the cumulative exposure likelihood index for the individual soldiers have been calculated, the individuals can be ranked according to their level of exposure. This ranked list can be used to identify individuals to be assigned to the low and high likelihood of exposure cohorts who are at the extremes of this gradient or spectrum. While it might be possible to have a more detailed gradient of likelihood of exposure, such as low, moderate and high, in order to provide dose-response estimation, it is perhaps desirable in this study, because of the imprecise nature of the exposure likelihood index, to identify only two groups, those at the two extremes of the index. These groups would provide the maximum achievable separation on likelihood of exposure, and minimize the possibility of misclassification between the two levels.

Recommended Procedures

Mr. Richard Christian (Chief of the Research and Rulemaking Branch, Department of the Army) has the most experience and expertise regarding the records of both Agent Orange use and troop movements. Therefore, we recommend that a set of criteria be sent to the Agent Orange Working Group for each of the steps outlined above to be transmitted to Mr. Christian and his group who will do the actual record searches. A summary of the steps, some of the types of records available and the outcome of each step is given in Table 1. In order to insure that the limitations of the exposure likelihood index which will be important in developing the analysis and interpreting the results are thoroughly understood, we recommend that a member of the investigative staff of the one coordinating center work closely with Mr. Christian and his staff in obtaining the information and lists from which the final selection of membership in the two cohorts will be made. Placing the responsibility for obtaining this information on the Agent Orange Working Group will facilitate as rapid a response as possible and will also provide the benefit of their considerable expertise and experience with the problem of developing a protocol for the study of the possible health effects of Agent Orange. Upon obtaining this information from Mr. Christian and the Agent Orange Working Group the coordinating center can establish the cut points for the

gradient of exposures based on the range of values, the number of troops entered into the gradient and the number of individuals needed for each cohort.

In order to reduce costs and reduce the time required to complete the exposure likelihood index, we recommend that after the completion of the review of MACV records the locations of all identified uses of Agent Orange, including those in the HERBS tapes, be plotted on a computer map of South Vietnam for month-by-month time intervals so that areas of high and low usage can be identified and further efforts and record reviews can be directed to the most likely areas for achieving maximal separation between high and low exposure groups. Also, as previously mentioned, the identified aborted missions and accidents involving Agent Orange should also be thoroughly investigated. The entire process of developing an exposure likelihood index could be greatly simplified if one or more of these situations is clearly linked to exposure of a sizeable number of groundtroops.

If, after the completion of work on the development of the exposure likelihood index, it is not possible to identify comparable groups with clearly different exposure likelihoods, then the study should not be implemented.

Table 1 Summary of procedures for selection of participants

	Selection procedure nodal points	Records available	Activity	Outcome
A.	Selection of areas of highest and lowest air spraying and exposure	HERBS Tapes, fixed wing abort mission records, likelihood of perimeter spraying, eg MACV records, chemical unit records	Review for areas frequently sprayed and never sprayed by dates.	Identify areas frequently exposed and never exposed (or infrequently)
B.	Selection of companies for development of exposure likelihood index	Military movement records, eg, Battalion S3 records, situation reports	Review for time and place of company headquarters in identified areas	Identification of companies for exposure likelihood index development
C.	Determination of company specific exposure likelihood index	A & B above	Integrate agent Orange use and company location data	Company specifics exposure likelihood index
D.	Selection of possible participants	Morning reports, personnel records	Review for company members present during company time of interest	Identification of personnel for person specific exposure likelihood index
E.	Determination of person specific exposure likelihood index	C & D above, records of other companies in which individual served	Integrate day by day company specific exposure index and personal day by day presence or absence in company	Person specific exposure likelihood index
F.	Selection of participants for study	Exposure likelihood index determined in E above	Order potential participants by exposure likelihood index, select from appropriate percentile ranges	Selection of veterans to be followed up and invited to participate

4. Establishing cohorts

Group Comparability

During the development of the exposure likelihood index, the records of battalions selected in areas of high and low probability of exposure (for which company records will be abstracted) should be searched for evidence of general comparability on important possible confounders. The initial selection of battalions should attempt to achieve as much comparability as possible on other concurrent exposures in the high and low Agent Orange exposure groups. Other concurrent exposures should include geographic areas, time period, types of combat activities and known use of such things as riot control agents, insecticides, antimalarials, insect repellants and antifungals. For example a battalion which provided mostly jungle patrols in the Delta region would be more likely to be exposed to insecticides, insect repellants and antifungal agents than one which operated in the less heavily forested areas of the Central Highlands.

Final Criteria for Selection of Individuals and Individual Comparability

Once the individuals with high and low exposure have been identified according to the exposure likelihood index,

the individual personnel records in Saint Louis must be abstracted for information on other Vietnam service, prior medical history, enlistment characteristics, service history, MOS Classification, and discharge status. Until the completion of work on the exposure likelihood index, it will not be possible to specify any type of possible sampling plan because the nature and size of the potential groups are unknown.

To estimate the effect on health of exposure to Agent Orange, the two comparison groups must be as comparable as possible on other factors which potentially affect health outcome. A variety of demographic and personal factors, including age, race, socioeconomic status and educational level, have been clearly established in a wide variety of epidemiologic studies as factors which may influence health status. In addition, volunteers have been shown in several epidemiologic studies to have a different health status than nonvolunteers. From our discussions with DOD personnel, it appears very likely that there were differences between the types of individuals who made up rifle companies and those who made up headquarters companies. There also were probably major differences between individuals in noncombat units and in combat units. We would expect there to have been major differences between

those individuals who served one tour of duty in Vietnam and those who reinlisted for multiple tours of duty. Therefore, comparison of volunteers tc draftees, of combat to noncombat units or of reinlistees to one-term servicemen would probably be confounded by differences in demographic and personal characteristics as well as other possible factors associated with these different types of units.

The development of an exposure likelihood index will be complex even for an individual who served only one tour of duty. It would be much more difficult to construct an index for an individual who served more than one tour of duty. The individual who served more than one tour of duty is also much more likely to have been exposed to Agent Orange sometime during his Vietnam service than the individual who served only one tour. Thus, while the individual serving multiple tours of duty could have the highest likelihood of exposure, the identification of a comparable group with multiple tours but low likelihood of exposure may well be impossible. Officers probably represent the extreme of this problem since they were most likely to have multiple tours of duty and to have served in a variety of both combat and noncombat situations.

For the reasons outlined above, our recommendation is to restrict the study to men serving 13 months or less in Vietnam and 3 years or less in the armed services. These men would offer the greatest probability of achieving a clear separation between high and low likelihood of exposure groups which are also comparable on a variety of personal and demographic characteristics, which otherwise might potentially confound the comparison of these groups. However, all members of a company or other relevant unit could be included in the initial exposure likelihood index and followed through records of their service in Vietnam to develop a complete exposure likelihood index for them. This would allow investigation of the possiblity of identifying a large enough group of high and low likelihood of exposure individuals comparable in other factors among those with multiple tours of duty, including officers, for inclusion in the ultimate study. This would, of course, require much more extensive and costly record review.

If a sufficient number of individuals is identified in the high and low likelihood of exposure groups it might be possible to individually match each high likelihood of exposure soldier to a low likelihood of exposure soldier on several important characteristics particularly age, race and socioeconomic status at entry into the armed services. Such matching could be done by existing computer programs but would add considerably to the cost of the study. Any

possible confounding factors should be examined and if necessary handled by stratification or adjustment techniques in the analysis of study results.

We have considered the possibility of including cohorts of women in the study. Final judgement should be made after the review of records for the exposure likelihood index. DOD has been unable to supply us with accurate records on the number of women who served in Vietnam. However, we have been told that the number was relatively small. Therefore, a meaningful study of them is not likely to be feasible.

If there are sufficient numbers of non-combat troops who have high and low likelihoods of exposure, consideration should be given to stratifying the high and low likelihood of exposure cohorts into combat and non-combat groups. This would allow examination of the joint effects of Agent Orange exposure and other factors associated with combat.

5. Examination Procedures

a. Introduction

The detailed literature review included in Appendices C-G (summarized in Section II of this protocol) have been considered in constructing the data information forms recommended for pilot testing. While the most well established health effect in humans appears to be that of chloracne, there are a wide variety of other effects suggested from human studies and established in one or more animal species. These effects include liver disorders, renal abnormalities, immunologic effects, reproductive effects, and a variety of cancers (particular soft tissue sarcomas in humans). Because of the few epidemiologic studies on human effects, and particularly because of the unique nature of the Agent Orange exposure in South Vietnam, there exists the possibility of a variety of unanticipated health effects as well. For these reasons, the testing of the study cohorts must include methods for detecting those conditions which have been suggested by the literature as well as methods for detecting unanticipated health effects.

The procedures to collect data from all members of the high and low exposure likelihood exposure cohorts should include 1) a questionnaire to elicit demographic factors and occupational and residential history, an exposure history to chemicals including herbicides, a Vietnam service history, and a complete medical history. 2) a complete physical examination including a detailed neurologic examination, 3) a series of laboratory tests designed to complement the physical examination, 4) a psychological test battery and 5) a battery of neuropsychological tests.

The following subsections describe the various instruments and test batteries which we recommend. All are more extensive than would be practical for a large cohort study but should be completely tested in the pilot study. After the pilot study, these data collection procedures can be modified as necessary. None of the data collection forms have been put in a self-coding format although the final instruments should be. The range of responses in the pilot test should be examined before final revisions and coding schemes are completed.

The procedures should be standardized and the information collected on standard forms. The adherence to standard procedures should be monitored by the study office. Information collected can be validated using a number of different procedures. Both the participant and those members of the study staff responsible for data collection, the physical examinations and laboratory tests must be blinded as to the exposure status of the participant. Details of the standardizing and validating procedures are given in section III B 9.

b. Suggested Questionnaire

A suggested questionnaire suitable for pilot testing follows below. In the development of this proposed questionnaire for the pilot test, we have drawn liberally from the questionnaire developed for the Australian Veterans Herbicide Studies and the United States Air Force Health ("Ranch Hand") Study, as well as from other studies which sought information on the general health history of males. We have also added questions and sections which we feel provide important additional information and have modified some questions to make them more appropriate for our target population. The questionnaire has been reviewed and formatted by the UCLA Survey Research Center. This center has extensive experience and expertise in the development and administration of interview schedules.

Questions were drawn from the Australian Veterans Herbicide Study in particular for two major reasons. The first was that we felt it appropriate to draw on the expertise of the Australian group which has taken more than two years to develop this draft questionnaire for their Agent Orange study, and the second is to make our study as comparable as is feasible to that study so that some comparisons might be possible between the two studies. One of the major problems likely to face studies of the possible health effects of exposure to dioxin is the need for large sample sizes, especially for outcomes which are rare. By

using comparable data collection techniques for the two studies, it may be possible to overcome some of the sample size problems by cautiously combining data which was obtained in a similar manner. Similar findings between the two studies would, of course, increase the probability that a finding is real.

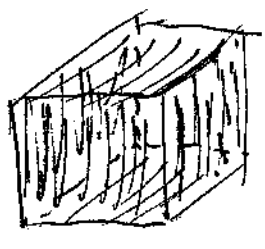
The questionnaire has been administered to subjects to identify poor questions, etc. On the basis of these, appropriate changes have been made where indicated.

The draft questionnaire has been designed to elicit 1) standard demographic information, residence, military and exposure histories, 2) information on possible confounding factors, 3) pre-existing and familial medical conditions, 4) conditions and diseases reported in the literature to be associated with Agent Orange, and 5) conditions and diseases which may be realted to exposure but which have not yet been reported.

The section on demographic and personal factors has been designed to provide 1) information on which to compare the two cohorts (eg, years of education, father's occupation etc), 2) information about exposures to hazardous chemicals including defoliants from occupational, recreational and other activities, 3) a military service history and 4) the participants perceeption of his exposure status with regard to Agent Orange in Vietnam.

The section on health status has been designed to provide information on perceived health status and conditions and diseases existing prior to and occurring since Vietnam service. We have included specific sections on diseases reported in the literature to be associated with Agent Orange but have also asked questions designed to screen for conditions not reported but possibly associated with exposure such as autoimmune diseases and respiratory problems. Questions have also been included on habits which may influence health status such as smoking, drinking and drug usage. These questions are included to permit comparison between cohorts of factors affecting health, and also to allow assessment of possible predisposing factors which may enhance the adverse effects of exposure. To provide the opportunity for validating reported conditions, and to uncover unreported conditions, medical release forms should be obtained for each source of medical care including the current physician.

The section on military service has been included to provide independent information (from that of the military record) of companies and areas in which the participant served and to provide a framework on which to report activities involving exposure to Agent Orange in Vietnam.



The questions on perceived exposure status to Agent Orange have been included primarily to permit us to evaluate the extent to which responses to the health history have been biased (consciously or unconsciously) by the respondent's perception of his exposure status (see Analysis Section for details.) The responses to these questions will also provide the opportunity to identify major misclassification. For instance, if large numbers of veterans from a particular time and geographic area thought to be unexposed, report the same information about their exposure to Agent Orange, this would constitute presumptive evidence of undocumented Agent Orange use.

Since a major question about the possible health effects of Agent Orange exposure concerns reproductive effects, considerable data on this area should be gathered. In order to accurately assess the male effects we feel that a questionnaire (also validated from medical records) administered to the spouse is mandatory. A suggested spouse questionnaire follows the main questionnaire. This questionnaire attempts to ascertain a complete reproductive history along with information on all important potential confounding factors. The best procedure (although more difficult, costly and perhaps less acceptable) would be to interview all former spouses as well as current spouses.

c. Physical Examination

The physical examination was designed to screen for possible abnormalities in all organ systems. This examination is adapted from that developed for the Australian study for the same reasons as for the questionnaire. In consultation with Dr. Dennis Cope of the UCLA School of Medicine, we have slightly modified the Australian form. Before pilot testing, the spelling of the medical terms should be "Americanized". The form for recording the physical examination follows below. The form was designed to require the physician to specifically check normal findings as well as abnormal findings to maximize the proper completion of the physical examination. The general physical examination can be completed by any general physician. The neurologic examination, however, should be conducted by a trained neurologist. As detailed in the quality control section, all physicians from the examination centers should be given a five-day training program in the administration of this particular examination to standardize the exam procedures and the conduct of the examination to the maximum extent possible.

Very subjective

The last portion of the physical exam form requires the examining physician to summarize his findings for each organ system and to express his level of certainty of these findings. Use of this technique would allow group comparisons on both certain and suspected abnormalities. As detailed in Section III B 14, the examining physician should be responsible for explaining any abnormal findings to the veteran and for urging or providing appropriate diagnostic or therapeutic follow-up.

d. Laboratory tests

The recommended laboratory tests are listed below in Tables 2 and 3. Those procedures indicated by an asterisk are those which must be completed in the examination center. All other laboratory specimens should be analyzed at a central laboratory facility. Procedures for blind split sampling and validation of the laboratories are detailed in the quality control section. The laboratory procedures were chosen to complement the physical examination, especially for organ systems suggested to be affected by Agent Orange, and to assist in detection of subclinical or impending conditions not easily found on physical exam. In addition, the procedures were chosen to provide a general screening battery for all organ systems for which laboratory tests are useful.

The procedures to be followed for drawing of blood and collection of specimens must be standardized. Training of laboratory personnel at each examination center in the proper techniques must be provided by the coordinating center. The schedules of examinations should be designed to permit mailing of specimens to the central laboratory for receipt by that laboratory within twenty-four hours of specimen collection. A responsible individual should be designated at both the data collection centers and at the central laboratory to expedite handling and shipping of specimens.

Rationale for Laboratory Procedures

1) Studies on the toxicity of TCDD in animals have shown that the following organ systems are damaged:

   a) Liver: Hepatic necrosis, liver enzyme changes, hypoproteinemia, hypercholesterolemia, hypertriglyceridemia.

   b) Reticuloendothelial system: Thymic atrophy, altered cellular immunity, decreased lymphocyte counts.

   c) Hemopoietic System: Anemia, thrombocytopenia, leukopenia, pancytopenia.

   d) Endocrine system: Hemorrhage and atrophy of adrenal cortex, hypothyroidism

   e) Renal: Increase in blood urea nitrogen.

   f) In addition, statistically significant increases in hepatocellular carcinomas (liver) and squamous cell carcinomas of the lung were found.

2) Studies on the toxic effects of TCDD in man have shown that the following organ systems may be damaged:

   a) Liver: Porphyria cutanea tarda. Increased levels of transaminase and of GGTP. Enlarged, tender liver, hyperlipidemia.

b) Renal: Hemorrhagic cystitis, focal pyelonephritis

c) Endocrine system: Hypothyroidism

d) Reproductive system: Infertility

3) Based on the reports of toxic effects in animal and human exposures, the following organ panels are recommended:

a) Hemopoietic

b) Reticuloendothelial

c) Renal

d) Endocrine

e) Neuromuscular

4) Hemopoietic screening should include:

a) hematocrit

b) Hemoglobin

c) RBC indices

d) Erythrocyte sedimentation rate

e) Platelet count

f) Prothrombin time

5) Reticuloendothelial system:

   a) White blood cell count

   b) Selective use of quantative immunoglobulin determination

6) Hepatic screen:

   a) SGOT

   b) GGTP

   c) Bilirubin, Total and Indirect

   d) Cholesterol

   e) HDL

   f) Triglycerides

   g) Urine prophyrins

7) Renal screen:

   a) Urinalaysis

   b) BUN

8) Endocrine screen:

   a) 8 AM cortisol

   b) FTI

   c) Fasting plasma glucose

   d) 2-hour post prandial glucose

9) Reproductive system:

a) Testosterone

b) Semen analysis

Additional Diagnostic Tests which should be Performed on All Subjects

Electrocardiogram - resting and following exercise on step stool

Blood Pressure - Right arm sitting

Chest X-ray - AP and lateral

Visual acuity

Nerve conduction testing - ulnar motor latency, ulnar fast velocity, ulnar slow velocity, peroneal motor latency and fast velocity, sural sensory latency

Routine spirometry - FEV_1 , FVC

Height

Weight

These are general screening procedures for the cardiovascular, respiratory and nervous systems. All must be performed at the examination centers. The electrocardiogram, chest x-ray, nerve conduction testing and spiriometry should all be interpreted at a central facility.

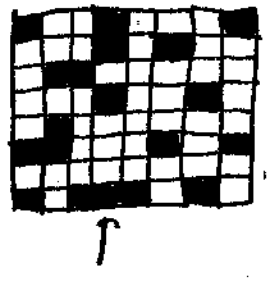
e. Psychologic Tests

The recommended psychological test battery which follows was developed by Dr. Carol Aneshensel of UCLA. The reasons for consideration of each of the 3 test batteries and their potential shortcomings are discussed. At minimum we recommend that the MMPI and the SCL-90 be conducted. The MMPI is a self-administered test and the SCL-90 can be administered by the interviewer who administers the questionnaire. The SADS-RDC would provide much more definitive diagnostic data and could be extremely valuable. However, this test must be administered by someone with at least the equivalent training of a masters degree in clinical psychology or medical social work and would thus be more costly. We recommend that the SADS-RDC be evaluated in the pilot test and the decision on its use in the full study be based on that experience.

f. Neuropsychologic Tests

The neuropsychologic test battery was designed by Dr. Francis J. Pirozzolo, Chief of Neuropsychology at Baylor University Medical Center. This test battery is recommended as a means to screen for subtle central nervous system toxic effects such as might occur from exposure to Agent Orange. The series of tests was designed to represent the most generally accepted and standardized neuropsychologic test methods. It was developed with the goal of producing a test battery which could be administered

by a trained technician and does not require the services of a neuropsychologist. However, a neuropsychologist must be a member of the coordinating center's staff and have responsibility for training the examining center technicians, supervising the continuing quality of their work, and interpreting of the results of this test battery.



6. Possible confounding factors

Confounding factors in epidemiology are those which may distort the apparent relationship between two variables under study. For example, in a study of the relationship between an occupational exposure and lung caner, cigarette smoking (a known cause of lung cancer) is a potential confounding factor. These confounding factors must either be similarly distributed in the different study groups or be appropriately handled in the analysis of the data. Similarity of distribution is the more desirable alternative since analytic techniques may be difficult to apply and only partially effective.

In the proposed study potential confounding factors include: exposure to other herbicides such as picloram or cacodylic acid; use of licit and illicit drugs; exposure to insecticides, and riot control agents such as CS tear gas; exposure to diseases (eg, malaria, cutaneous fungi); water supply, length of Vietnam service, and multiple tours of service in different geographic regions of Vietnam; pre or post Vietnam occupational history (including TCDD exposure); combat versus non-combat experience; educational level; race; rank, and service occupational classification (MOS). Length of Vietnam service, multiple tours of service and rank can be handled by the eligibility criteria specified in section III B 4. A list, more complete, of the potential confounders we have identified is included in Appendix I.

These potential confounders are assumed at the moment to be fairly equally distributed among similar units operating at about the same time in similar geographic and seasonal circumstances. Questions on the potential confounders are included in the questionnaire. All of these should be more thoroughly investigated during the development of the exposure likelihood index, both through the Army records of their use or occurrence, and through search of the DTIC files. Any of the potential confounders found to be unequally distributed between the two exposure likelihood cohorts should be examined in the analysis phase for the need for stratification or adjustment procedures.

7. Tracing of men selected for study

All possible effort must be made to identify and locate every man selected for this study. This is particularly important because both the exposure status and the possible adverse outcome may be connected with difficulty in tracing. Therefore, differences between high and low likelihood of exposure cohorts in the proportion of cohort members located could either obscure a real association or create an artifactual one. For example, a potentially highly exposed combat veteran may be both harder to find and more likely to have suffered an adverse effect than an accounting clerk stationed solely in Saigon with potentially low exposure who returned to a business career in the U.S. If it is easier to locate the unexposed and/or the unaffected, then any relationship of exposure and possible adverse effect could be obscured. On the other hand, if the combat veteran is concerned about his health and has filed a claim with the VA he may be easier to locate than the former file clerk who has gone to a private physician for medical care. In this type of situation a spurious association might be observed. (The examples given are deliberately extreme to illustrate the problem and do not indicate any specific opinion or information on exposure likelihood, or adverse effects from exposure.)

Tracing operations are expensive, time consuming and may be considered by some as invasions of privacy or breaches of confidentiality. The tracing protocol detailed here is designed to make maximum use of existing military, veterans, and public record sources first, going on to specialized data bases which may provoke more privacy and confidentiality concerns only after the first steps have been found unsuccessful. The sequential steps in the tracing protocol are detailed below:

a) Abstraction of existing military records of each selected serviceman in as much detail as is available from the record. This information should include: name in full, including any aliases known through the record; service number and/or social security number; birthdate and birthplace; sex; race and/or any ethnic identification; religion; marital status, including date of information, date of marriage if available, full name of spouse and any address information; next of kin data, including date of information, full name of next-of-kin, relationship to subject and address; parental data - same as next-of-kin; address of serviceman at induction; address at discharge; service details, including dates, assignments, job titles, in service training, medical information, disciplinary actions; and physical description, including height, weight, eye and hair color, distinguishing physical characteristics and any permanent or progressive medical states.

These data, and any other information found to be included in the military record and useful for tracing, should be abstracted onto master coding forms. The forms should be designed so that identifying information, such as names, addresses and service numbers will be stored separately from service or medical details. Linkage can be maintained in the data base management system through arbitrary number coding.

Data specified above for extraction have been selected to provide 1) tracing routes (addresses, names of spouse, kin, etc.), 2) information necessary for tracing through data sources and in data bases (birthdate, social security or serial number, etc.), 3) indicators for further tracing activity (medical information, service training, disciplinary action, etc.), and 4) information useful to verify that the veteran located is the correct one (height, eye color, permanent distinguishing characteristics, etc.).

Some members of the selected exposure cohorts will be "located" at this step, including those who died in service, those still in service and those still serving military prison sentences. Their identification is direct and they will be transferred to the study file described in the last paragraph of (b) below.

b) Establishment of a computer based data management system incorporating data collected in step one with provision for addition of information derived from further tracing procedures. This system 1) would provide the basis for tracing procedures, 2) can be used to provide computer readable or hard copy lists of selected subgroups, ordered as required, for use by agencies or organizations assisting in the tracing, 3) can keep track of tracing procedures already used, the procedure currently in progress and, when appropriate, a success indicator along with status and fact of location of veteran.

To assure privacy and confidentiality, necessary identifying information and the actual location of the traced veteran should be incorporated in a separate computer file for study use; the actual address should not reside in the tracing file.

c) Utilization of Veterans Administration records. All VA data sources, data bases and benefit providers should be queried for the most recent contact with members of the two cohorts. Data forms must be provided for recording of the specific contacts, the most recent location of the veteran and the date of that information. Records to be searched include: benefits - such as education, housing; disability, especially pensioners; medical services; Agent Orange register; complaints registers; death benefits; any other veterans services provided.

The ordering of these searches should be determined both during and after the pilot test in consultation with the VA to maximize the yield of any given search. The existence of VA data and the file location of that data should be identified in most cases from the Veterans and Beneficiaries Identification and Records Location System (BIRLS) file. Other VA computer files may only need to be searched occasionally. Those veterans identified as deceased in BIRLS can be eliminated from further tracing. The parameters which determine the usefulness of any type of VA file such as the date of the file or the type of file (eg, pension versus educational benefit) should be examined in the pilot test.

d) Cooperating Veterans organizations: Veterans not located through steps a or c above, or whose most recent identified location is no longer current, should be sought through cooperating Veterans organizations membership or contact rosters. To avoid privacy problems, the fact and date of location could be obtained from the organization. Actual initial contact could be made by the organization with study contact only after consent by the veteran.

Unit-related military service organizations, such as the "Big Red One," can be queried for location of veterans eligible for membership in the same way as the more general veterans organizations.

e) Letters to the veteran at the last known address. This address could be the induction address, the discharge address, or an address obtained through a, c or d above. While this letter should be used to locate or to confirm the location of the veteran, it can also be structured to advise the veteran of the study, his selection for participation and to initiate the recruitment process by enclosing the initial contact letters (see Section III B 8).

The first and second mailings of this letter should be by ordinary mail with a prepaid request for notice of address correction. The third letter should be by certified mail, return receipt requested. Non responses can be referred for field check by study staff or by a tracing agency such as Equifax. Returned mail should result in further tracing steps.

f) A field check should be done in those cases in which mail is neither answered nor returned. The first step in such a check should be by telephone, utilizing both usual and reverse directories to obtain telephone numbers. If this procedure is not effective, a field visit to the house should be made by study staff or a contract organization to ascertain if the veteran does indeed live there. If not,

the field check could then be extended to neighboring houses to gain any information possible about the veteran, his present whereabouts, the date of his most recent residence there, etc.

It should be noted that steps e and f can be re-utilized as a followup for all later steps resulting in an address for the veteran. They can be repeated each time an address is obtained.

g) Letter to spouse or next of kin. This tracing should proceed in the same way as step e if the spouse or next-of-kin address is different from that used in step e for the veteran, and if the veteran has not been located.

h) Motor vehicle operators registration and motor vehicle registration. Motor vehicle bureaus in the last known state of residence, nearby states, sunbelt states and other states experiencing large population growth should be queried for operators licence (or vehicle registration) information including address. The computer tracing data system should include information on states queried so that inquiry is not repeated. Addresses obtained should be verified through step e above.

i) Retail credit checks through Equifax or similar organizations. Again, locations obtained should be checked through step e procedures.

j) Social Security System checks for last employment date, disability and retirement status. Unfortunately, the system for the still employed is sufficiently out of date that the information is not current. It is current, however, for those receiving benefits, and even 3 year old information may be more useful than 10-15 year old information. The information will also be useful to ascertain employment record and therefore some measure of stability, hence locatability.

k) Internal Revenue Service for filing and address information only. This file is current within one year plus time to computerize. If the NIOSH waiver can be obtained for this study, the IRS files should be one of the first tracing resources utilized, ie, for those not located after step 3 above.

l) FBI (and other law enforcement agencies) record searches. These types of agency records could be searched for contacts with the selected veterans, present location if serving sentences or on probation status, most recent address and date of information if not.

m) National Death Index. While the BIRLS file should be virtually complete through 1981, it is likely to be less complete in subsequent years because of the recently enacted law reducing the burial benefit. Thus, for veterans who cannot be located by the above steps, a search of the National Death Index should be performed to identify deaths not in the BIRLS file.

Note that this source should be used only for those not located in steps a-l above.

n) Advertising for whereabouts, particularly in publications likely to attract the group not located through steps a-m above. This group can be characterized through information in the computer derived from the military record and the results of the tracing steps and an appropriate advertising campaign developed at that time. Such advertising could, for instance, take the form of television spots, advertisements in major newspapers or advertisements in so called underground newspapers. The size and scope of such a campaign would also depend on the number of veterans still remaining unlocated, and on confidentiality considerations.

8. Subject contact procedures

After the completion of tracing procedures (see Section III D 7 for details) the subjects will be identified as either a definitely identified and located individual or a located individual of a correct name but with some uncertainty as to whether it is the correct individual. Each subject identified in either category should be first contacted by a letter from the coordinating center which outlines the purpose of the study, encourages the participation of the individual and specifies that a follow-up contact will be made by telephone. A suggested draft of this letter is shown in Figure 2. Along with this letter from the coordinating center, it would be helpful to enclose a letter encouraging participation from the President of the United States, if such a letter can be obtained. For any subjects for whom a telephone number is not available a postcard should be enclosed with the letter which asks for the current telephone number so that the individual can be contacted.

At the time of mailing of the letter, the individual data collection center closest to the subject should be notified of the mailing and given the subject's current address and telephone number (if known). Within a 10-14 day period following the mailing of the introductory letter, each subject should be contacted by telephone by a specially trained staff member of the data collection center. This

staff member should be familiar with the study so that he or she can answer questions that the subject may have about the study. The telephoner should also ascertain verifying information at the time of telephone contact for any subjects whose identity is in doubt.

At the time of this telephone contact, the interviewer should try to schedule an appointment for the subject to be examined at the data collection center. The interviewer must be familiar with mechanisms of transportation in that geographic region to be able to assist as necessary in arranging transportation and/or lodging for the subject. In the case of veterans who refuse participation, the interviewer should try to ascertain the reasons for this refusal and possible ways to overcome the objections. If the veteran is willing, a shortened questionnaire should be administered by phone at that time.

For subjects who return a postcard with their telephone number, the procedures above would be used. Subjects who do not return the postcard must be contacted by field visit. The field visit should be conducted in similar fashion and for the same purposes as the telephone contact.

FIGURE 2

Suggested Initial Contact Letter

Dear Subject:

As you are aware, many veterans who served in South from exposure to Agent Orange. The government of the United States is also concerned about this problem and has asked that a study be done to ascertain what health effects may have occurred from Agent Orange exposure so that appropriate treatment and compensation can be provided. We are conducting that study for the government.

Your name has been selected by a scientific process to represent veterans who served in South Vietnam. Many of the veterans chosen we believe not to have been exposed to Agent Orange, while many others we believe were exposed to Agent Orange. You may have been chosen to represent either of these groups. As the attached letter from the President of the United States indicates, this study is considered to be of vital concern to the people of the United States, particularly the veterans who served in South Vietnam. Therefore, we strongly encourage your participation in this study.

In the next few weeks, a member of the examination center closest to your home will call to explain the study to you in more detail and answer any questions you may have about your participation. Briefly, the examination will consist of a questionnaire which will ask you about your illnesses and hospitalizations, about your reproductive experience, about your service in South Vietnam, and about a variety of other questions which may relate to your current health. Whether you have been selected to represent the group believed to have been exposed to Agent Orange or the group believed not to have been exposed to Agent Orange, you will be given the opportunity to express your own knowledge about possible exposure of which the study may not be aware. The rest of the examination will consist of a complete physical examination with blood and urine testing and a variety of special test procedures designed to evaluate different body systems.

All information which you give in this study will be kept strictly confidential, to be utilized only for the group analysis of study results. The information will not be part of your VA records unless so requested by you, and will not be disclosed to any government agency or any other agency or individual without your expressed written consent. You will, of course, be notified promptly of any abnormality which is detected during the examination. If any abnormalities are found, you will be given assistance in

securing further evaluation of the problem as necessary from either the Veterans Administration or your private physician. You may have the results of this examination sent to the Veterans Administration or your own private physician upon your written request.

Sincerely yours,

IHA Supervisor

9. Quality control

The ultimate value of the results of data analysis from any study is dependent upon the quality of the raw data going into that analysis. Potentially damaging errors can occur in the data set at any stage of data collection. Such errors are frequently the result of misunderstandings, lack of care in the recording of data or inappropriate application of individual judgement. The possibility for errors is particularly strong when multiple data collection centers are utilized as in this study. The control of such errors can be achieved through the use of a variety of techniques, such as rigid criteria for the recruitment and training of study staff members, the careful standardization of all study procedures, blinding of staff as to the exposure status of individual subjects, and utilization of procedures for double checking at least a sample of the work of staff members. Individual quality control procedures for each of the critical steps in the data collection are discussed in the following paragraphs.

a. Selection of cohorts

Part of the task of constructing the exposure likelihood index will be to select for study those situations in which the likelihood of exposure to Agent Orange can be most clearly documented and those units with the most complete and careful records of troop locations and individuals present. In addition, when the actual selection of individuals for study is accomplished, the individual personnel records (predominantly from St. Louis) must be checked with the unit records from South Vietnam for consistency. Such a comparison can be made by a computer program which can be developed during the pilot study. This program would match dates and units from personnel files against those from the South Vietnam unit records. Individuals with discrepant information in these two files should be rechecked for obvious errors which would explain the discrepancy. Further checking would be necessary to locate less obvious errors. If the discrepancy is not explained by these checks, these individuals would be eliminated from the study.

b. Record abstraction

The basic data set for the early phases of the study will be based on abstracts of the army unit records from SVR and the personnel files. Abstracting should be done by trained study staff members who review the records by hand and record the information on standard forms. A sample of these abstracts chosen by a predetermined sampling algorithm should be reassigned to another record abstractor for complete reabstraction. The abstract records from each abstracter can be compared in a simple list program on the computer for any inconsistency. Inconsistencies should be referred to the abstracting supervisor who can investigate the source of the error and bring the error to the attention of the appropriate abstracter. Any abstracter found to have substantive errors on more than five percent of abstract forms after two attempts at retraining that individual should not be retained in this aspect of the study.

Additional quality control can be achieved through the application of careful standards for recruitment of abstracters. These criteria should include demonstrated intellectual abilities at a level sufficient to understand the abstracting procedures and demonstrated careful and consistent clerical abilities. The training program for the record abstracters should include a full discussion of the need for careful abstracting, the effect on the study of errors in abstracting, instruction in writing numerals, a

careful step-through of each form to be encountered in the records, supervised abstracting of a selected series of records which illustrate the types of forms and potential problems to be encountered in abstracting, and the independent abstracting of a series of selected training records which have been carefully preabstracted by the abstract supervisor.

c. Tracing

The primary difficulty which might be encountered in tracing is the identification of the wrong individual. This problem can be minimized by the use of matching criteria utilizing a short series of question responses obtained from the potential subject at the time of the initial telephone contact. Information which would be useful for such criteria include birth date, full name, parents' names, Social Security number or service number, and unit assignment and date in SVN and any distinguishing physical characteristics. A positive match for purposes of proceeding with recruitment could be the determination of any three of these six data points. The rate of mismatches detected at the time of examination should be monitored. If a mismatch rate of greater than one percent is detected, the system should be reviewed to determine the cause of the high mismatch rate.

d. Interviews

Rigid criteria for the recruitment of interviewers and a standardized training program must be developed. The manual used by the UCLA Survey Research Center is included in Appendix J. The manuals from the University of Michigan Survey Research Center (4) and the Public Opinion Center (5) may also be helpful. Further information on training procedures and supervision of interviewers can be found in the discussions and in the references included in references 6 through 14 bibliography. The interviewers from each examination center should undergo a two week training session conducted at the coordinating center. The training program should include: 1) discussion of the study design, rationale and procedures; 2) explanation of the need for following exact procedures in conduct of the interviews and recording of data; 3) an opportunity to comment on the questionnaire and interview procedures in a constructive manner; and 4) supervised practice interviews of at least five volunteer "subjects" (each of the questionnaires so completed should be gone over with the interviewer by the interviewer training staff).

Each questonnaire completed by the interviewers must be checked by a coder/editor for accuracy and completeness; errors should be brought to the attention of the interviewer and the interviewer supervisor. (If the number of interviewers in an examination center is more than three, an interviewer supervisor for that center should be selected.) The interviewer supervisor should be responsible for retraining as necessary and for releasing interviewers who repeatedly are unable to complete interviews accurately. In the early stages particularly, and from time to time during later stages, the interviewing supervisor should sit in on a randomly selected interview to observe the conduct of that interview and the adherence to the expected protocol.

The interviewers must be kept blind to the exposure status of the individual subject as far as possible. The questionnaire has been designed to help maintain blinding by placing the exposure questions towards the end of the questionnaire following the collection of outcome variable data. A final standardizing technique for the interviewers should be to train one or more "dummy" subjects who can be scheduled, unknown to the interviewer, for interviews as study subjects. These individuals should be trained to give a predetermined set of answers to be checked against the recorded answers by the interviewer and in addition they can observe the interviewer for aspects of the actual conduct of the interview.

The actual data in the questionnaire itself should have several quality control procedures applied. Several questions are repeated during the course of the questionnaire and can be used to obtain a measure of subject reliability. Several questions in the questionnaire ask for data which is recorded in the personnel records (eg, dates, units, locations served in SVN). The data from the questionnaire in the personnel record files can be checked for consistency. If major discrepancies are found a specially trained telephone interviewer should recontact the subject to gather additional information which can help to determine the source of the discrepancy.

Validation of medical data in the questionnaire will rest in part on the examination program. For instance, a report of shrapnel wounds of the leg can be validated by checking results of the physical exam. Additional validations should be done of the reported medical conditions in the questionnaire. Each subject will, according to the proposed questionnaire, be asked to sign a release of medical information form and will be asked for the name and address of the diagnosing physician for all reported medical conditions. The diagnosing physician in the case of all diagnoses of interest to the study should be sent a questionnaire asking for the details of that diagnosis and, of course, for verification of that diagnosis. Each subject will also be asked for the name and

address of his regular physician. This physician should be sent a general questionnaire which asks about medical conditions and which includes a list of conditions of interest to the study. The use of this general questionnaire along with the specific questionnaires to reported diagnosing physicans would allow the estimation of both under and over reporting of conditions.

e. Coding and editing

The individuals doing coding and editing of questionnaires, including the validating questionnaires from physicians, should have the same standardizing procedures for recruitment and training as for the record abstracters in Section b above. In addition a random sample of five percent of the questionnaires should be recoded and reedited by a separate coder-editor and any discrepancies brought to the attention of the supervisor.

f. Physical examination

The physician or physicians in each examining center, to be assigned to this study, should be selected for their interest and abilities in physical diagnosis. These physicans must be kept blind to the exposure status of the subject being examined. All selected physicians should be given a 5 day training course at the coordinating center or the examination center for the pilot test. This training course must emphasize the necessity for carefully standardized conduct of the physical exam and must review in

detail each examination procedure. The examiners manual (15) developed by the Australian study team should be valuable for developing this training program. The training program should also include the independent examination of several trained "dummy" subjects so that inconsistencies among physicians can be detected and discussed.

The actual conduct of the physical examination can be standardized by the use of the standard physical examination form. The form includes a specific checkoff of all normal parameters. This requirement should help to ensure that all exam procedures are, in fact, followed. Each physical examination form must be reviewed by a coder and editor for completeness. Any detected incomplete sections, apparent errors or inconsistencies on the physical examination forms should be brought to the attention of a supervising physican from the coordinating center. The same dummy interview subject used to check on the interviewers can also be used as a check on the physician examination procedures. This individual can be moved fom site to site to assure intersite consistency.

g. Laboratory tests

Laboratory tests represent some of the most objective outcome data to be gathered in this study. To be of maximal value, however, they must be very carefully standardized. All laboratory procedures which can be done at a central laboratory, ie, those not affected by time delays between collection and analysis of the specimen, should be performed at a central laboratory. This procedure would at least ensure comparability for analysis of specimens collected fom different examining centers. In addition, a random five percent sample of all laboratory specimens should be sent to the laboratory in the form of blind split samples. This would allow the calculation of reliability or repeatability of the procedures. The laboratories of the Centers for Disease Control, or another standard laboratory as appropriate, should be brought into this study for validation of the study laboratory procedures. This validation should consist of the regular submittal, as subject specimens, to the study laboratories of standard specimens analyzed at the reference laboratory. The results from the study laboratory would be compared for accuracy to the value from the reference laboratory.

For those procedures which must be done in the laboratory of the examining center, the laboratory personnel should be carefully trained by a reference laboratory in a standard procedure to be followed. Wherever possible, the specimens of the random 5 percent sample should also be submitted to the examining center laboratory as blind samples for reliability testing, along with known or standard specimens for those tests from the reference laboratory for validity testing.

h. Key entry

Key entry of data should be done using an edit program based on a data management programming system such as SAS, RAMIS or SIR. This can be done by trained key entry operators on site (either through terminals linked to a central computer, or onto a local compatible computer with portable output readable by the central computer) or by study staff at a central computer facility. Centralized data entry would be much easier to supervise. Verifying should be done at a 100% level. Non matches should be referred to a key entry supervisor. Unacceptable error rates (ie, greater than 1%) following retraining should require replacement of the key entry operator. Part of the training of interviewers, coders and editors should include instruction and practice in numeral and character writing to remove one major source of key entry error.

i. Computer editing

Following key entry and verification, data must be computer edited for acceptable values of variables and for cross-variable inconsistencies and incompatibilities. Such problems should be printed out and referred back as necessary (key operator, coder, interviewer, examiner, subject) for resolution.

10. Data Management

The data management protocol for a study of this size and cost is a crucial factor in the success of the project. It includes study control, data capture designs and documents, establishment of data bases, quality control and preparation for analysis. The phases of data management necessarily parallel those of the protocol as a whole and are divided, here, for purposes of discussion as follows:

a. exposure likelihood index development and identification of exposure groups

b. identification of individuals in selected exposure groups

c. location of individuals

d. recruitment, scheduling of examinations

e. interview examination, follow-up advisories

f. collection of validation material

g. analysis

h. notification of assumed exposure status and study results

These are several general principles and assumptions underlying this proposed data management protocol. 1) We assume that data management operations will be based in a central computing facility equipped with a large scale main-frame computer such as the IBM 3033. With hundreds of variables on at least 12,000 subjects, data base management and data analysis would be impractical on a smaller

computer. The computer should be equipped with the appropriate peripheral equipment and system including the capacity to interact with remote, non-hard-wired terminal entry. 2) There will be a primary data base management system employed such as RAMIS II. (RAMIS II is a proprietary product of Mathematica, Inc. Princeton, NJ). A description of features of RAMIS II from the 1980 version of the Users Manual is included in Appendix K. Another system incorporating these features could be substituted; the following discussion of data management is predicated on the use of a system equipped to handle hierarchical files with maintenance of logical relationships among data files and elements, logging of data transactions and the potential for access of non RAMIS files. 3) Data will be manipulated as little as possible prior to computerization. 4) Self-coding data capture documents will be used as fully as possible. 5) The data management system must be capable of updating and editing the data base files. 6) The data management system must be capable of linking the various files from different data sources. 7) The data management system must be capable of limiting access to different files to those individuals with a need to know.

If any of these assumptions are not appropriate for the facility designated for the study, certain adjustments will then be needed in the protocol in terms of developing IBM compatibility, designing and writing data base management programs or adapting this protocol to other existing systems, etc.

In the following discussion, sections a through f, the use of the computer in assisting in data collection is discussed. Because of the large sample size and the complications involved in determining a sample frame, this computer use is advisable.

a. Exposure likelihood index development and identification of exposure groups. Much of the necessary data for this activity already exist in computer readable form in the HERBS tape. Additional data on helicopter spraying activities, ground spraying, herbicide storage and air or ground accidents involving Agent Orange must be identified and computerized by location and date of exposure to match the HERBS tape format.

After identification of high and low time-space areas in SVN, companies operating in the specified time-space areas should be identified. Locational data from these companies should be computerized with time and space coordinates.

The time-space files of exposure and company data should be compared to assign day-to-day exposure likelihoods for the companies. (see Section III B 3 above).

Identification and inspection of the existing Army records is required before appropriate data capture documents can be developed. We recommend that data management specialists with the study observe the military information specialists as they locate the needed information so as to develop instruments that will capture the needed information - minimizing both hampering the abstractor or slowing the computerization process.

b. Identification of individuals in selected exposure groups. Company records, including morning reports and operation report lessons learned, etc., for companies selected will have to be reviewed for personnel acquisitions and losses, both temporary and permanent. Names and service or social security numbers should be computerized, along with dates and character of listed events (arrival, departure, leave, illness, MIA or KIA, etc.) relevant to presence or absence in the area at a specific time. These data should be linked to the data file from step A above for each individual and his exposure calculated based on his presence and his company's daily exposure index. After calculation of the index for each person, individuals should be ranked by exposure likelihood and identified for follow-up or exclusion as per study protocol.

A basic computer file of persons selected to be followed should be created at this step, and used as the base file throughout the study. This file should include name, service or social security number, time in company and exposure likelihood index.

A second file of day-by-day exposure levels and dates should also be maintained on all persons identified for follow-up. This file should be linked later to the questionnaire information obtained on exposure so that comparison of assumed and perceived exposure can be made.

c. Location of individuals. The basic file created in B above should be used to identify individuals to be located. Tracing procedures are detailed above in section III B 7. The computer data management system should be used to direct the tracing procedures to be used, to keep track of procedures which have been used, to record the outcome of tracing and to transfer located individuals into the appropriate files for follow-up:

1) Located free-living - recruit for interview and examination

2) Located in institution - appropriate follow up depending on nature of institution (the computer can identify these for human decision)

3) Located, deceased - follow up for available medical records.

All locational findings, including acceptance of loss to follow up should be transferred back to the basic file (B) as provisional endpoints (located, living) or as final endpoints (deceased, unable to follow).

These subfiles can be utilized and modified as information is received from further procedures and activities.

Information for the location procedures should be gathered as described in the training section (III B 7). The St. Louis records will provide the major quantity of this information which should be abstracted onto self-coding forms. The design of these must be based on both the format of the files and the customary procedures in using those files in the St. Louis center. (Neither part of this necessary information is available to us at this writing.) The information to be abstracted is specified in section III B 7.

These data should be transferred to the computer file created in B. The computer can then scan the material and direct the next appropriate step in the searching strategy outlined above. Regular updates of searches underway should be available, as should information on levels of success at each step, number of steps necessary to locate, etc.

The outcome of each step for each individual should be entered into the computer record as it becomes available.

Individuals successfully traced, should be entered into the appropriate follow-up sub-file.

d. Recruitment, scheduling of examinations, interviews. The follow-up sub-files developed in C above should be used to direct recruitment and scheduling. The closest examining facility should be identified for each individual, and that site notified to proceed with recruitment and scheduling. The file on each individual should be kept open and the site queried on a regular basis until recruitment is completed and the examination scheduled for compliant individuals. Refusal or deaths should be noted in the recruitment file and transferred back to the basic file as an endpoint achieved.

Following scheduling of examination, sites should be queried regularly, using a system like the reports preparation system of RAMIS II, until the examination is completed and data received at the central facility. After information is received, the individual should be transferred to the next file, with information on the completion transferred back to the basic file as a provisional endpoint.

e. Interview, examination, follow-up advisories. The interview and examination schedules are described and included in section III B 5. The forms are designed to be self-coding insofar as possible. Information from these forms can be key entered centrally or through remote on-site terminals, utilizing a system like the Record Management System of RAMIS II. In the pilot study other methods of data entry such as key punching or optical scanning could be investigated. In the case of key entry, the use of smart terminals with self-prompting entry and editing routines should also be investigated. The choice of entry system from cards, direct disk entry or tape should be evaluated separately for each major source of data. This management system should monitor intake; and entry should be 100% verified (or reentered) to assure a minimum error level.

Programs must be developed and linked to the data management system to identify individual responses or findings or patterns of responses or findings which require follow-up. These programs should be developed in collaboration with clinician members of the coordinating center at the start of the study so that they are responsive to the group being examined, VA resources and good current medical practice.

f. Collection of validation material. In the event that follow-up is required for reported health events not verified in the examination procedures or for ascertainment of time of initial diagnosis of a disease entity, individual records can be identified for such follow-up. The need for follow-up should be computer assisted. Again, periodic query of the examination center should be made until follow-up is either completed or declared to be impossible to complete.

The initial data capture form for these follow-ups should be a letter to the physician or hospital requesting specifics on the particular event and/or date of interest. As the study progresses, common areas of inquiry or common diseases may emerge; specific data forms can then be developed.

g. Analysis. A major function of successful data management is to preserve and present the data for analysis. The fully linked hierarchical files will be available on each individual, from his likelihood of exposure to validation of his childhood asthma. Clearly, this is too long, too complex, and too detailed a file for most analytic evaluation. The data management system should permit the selection of subsets of variables, of values within variables, and/or of individuals according to record characteristics for use in specific analyses. These data subsets can be created as needed according to specifications for individual analyses. These data subsets must be directly accessible by a variety of statistical packages such as BMDP, SAS or SPSS.

h. Notification of assumed exposure status and study results. As noted in the section on notification (III B 14), there is an obligation to advise the participant of the results of the study and what they might mean to him as an individual. Part of this notification would include his likelihood of exposure, and part might depend on responses and findings in the interview and examination. The computer based data management system should allow determination of an individual's report content. Personalized reports can be ordered for all participants, or for those determined to be at some designation of "high risk".

11. Data analysis

Analysis should be carried out in a series of steps designed 1) to identify the presence of missing or suspect values, 2) to evaluate the reporting bias present due to the participant's perception of his Agent Orange exposure, 3) to investigate which statistical methods are most appropriate for analysis, 4) to confirm the comparability of the high likelihood of exposure and low likelihood of exposure cohorts, and finally 5) to determine whether there exist diseases or indicators of bad health associated with high exposure to Agent Orange.

a. Quality of Data and Management of Missing and Unreasonable Values

The first step of analysis should be to assure that the data gathered are of the highest quality possible. Errors can occur at any of the steps between record location and putting the data into machine readable form. Several techniques that are easy to implement are available to detect these errors. The data must be screened for internal consistency. For example, several questions on the interview schedule require consistent answers. The results of laboratory examinations and the physical examination should provide additional opportunities for checking the internal consistency of data collection. In addition, reported diseases and conditions can be compared with the information obtained from the attending or current physician.

The data must be screened for missing values and values which are either lower or higher than is reasonable. Whenever possible, these values should be replaced with data from one of the other data sources (entry, service and discharge records; vital statistics; interview schedule; medical history; physical examination; and/or laboratory test results).

Information on the same factor obtained from multiple sources should be compared. Inconsistencies should be reviewed without knowledge of the status of the individual and a technique established whenever possible for resolving inconsistent information.

b. Relationship of Participant Reported Exposure to Agent Orange and Health Outcomes

A major concern in this study is that individuals will know their exposure category and, therefore, will give biased responses (either consciously or unconsciously) based on that suspected exposure. There are four groups of individuals for whom health outcomes can be compared which may provide an estimate of the amount of bias resulting from suspected exposure to Agent Orange. The high likelihood of exposure cohort will contain individuals who report exposure to Agent Orange and individuals who do not report exposure to Agent Orange. Likewise, the low likelihood of exposure group will also contain individuals who report or do not

report exposure to Agent Orange. Health outcomes can be compared (as described below) for these four groups. Comparison of findings between those reporting exposure but not verified to have exposure with those verified to have had exposure but not reporting exposure would provide an estimate of the amount of bias present due to the participants perception of his exposure status.

c. Statistical Methods Applicable to This Study

Univariate descriptive statistics using major packaged statistical routines can be applied to all data. These descriptions include simple histogram plots, box-whisker plots, and common summary measurements for the variables of interest. Commonly available packages such as BMDP, SAS and SPSS can be used for these descriptions as well as for later analyses suggested by the results of the descriptive statistics. These should include both univariate and multivariate techniques. Discrete data (measured on nominal and ordinal scales) can be analyzed by simple chi-square analysis and by log-linear analysis. For interval (continuous) data, logistic regression analyses can be used with a dichotomous outcome. The appropriateness of the logistic model can be examined by using goodness of fit criteria.

d. Comparability of Cohorts

The validity of the historical cohort design is dependent in large part on the assumption of comparability of the two cohorts with different exposures. Although the two cohorts will hopefully be chosen in a manner to make them as similar as possible on all important measures except exposure, it is extremely important to look for any differences that might affect the apparent relationship of exposure to health outcomes.

A first step should be to compare the response rates between the two cohorts. Some information will be available from entry, service and discharge records for non-respondents. Using information from these sources comparisons between respondents and non-respondents within each cohort can be made.

Demographic characteristics such as years of education, father's income, and characteristics of childhood residence should be carefully studied to see if any differences between the cohorts emerge. The two cohorts should also be compared for the prevalence of diseases or conditions present before entry into the military service. Other characteristics which should be studied include the prevalence of familial diseases or conditions, exposure to hazardous materials (including herbicides) outside of Vietnam, and type of military service including years of service and distribution of ranks.

Behavioral differences can also be examined. For example, the cohorts can be compared with respect to health habits such as smoking, drinking, use of marijuana, and the practice of the seven health habits associated with good health status and longevity (as outlined by Breslow) (16), if the data on these habits prior to Vietnam service can be reliably obtained.

Statistical techniques for these comparisons can include log-linear analysis and logistic regression, which can point out pre-existing variables that are associated with or can be used as predictors for exposure to Agent Orange. For example, using exposure versus non-exposure as the outcome variable, a logistic regression can help to determine if any differences exist between exposure to Agent Orange and demographic characteristics at enlistment.

e. Factors or Outcomes Associated with Agent Orange Exposure

The behavioral characteristics discussed above should also be examined in the post-exposure time period. Further analyses of association between Agent Orange exposure and health outcomes may need to be stratified or adjusted according to cohort differences in these characteristics.

A number of health outcomes can be examined. These include the presence of specific diseases or conditions, the results of psychologic testing, the results of laboratory tests, the perception of general health and the current occupational status. The search for health outcomes can be either adjusted for or stratified on any differences found between the two cohorts.

The screening procedure for investigating the relationship of specific diseases or health conditions with exposure to Agent Orange should include a screening of all health outcomes solicited. Special emphasis should be placed on looking for differences in prevalence of diseases or conditions reported in the literature to be associated with Agent Orange exposure. Careful consideration should be given to confounding factors which might decrease the likelihood of obtaining statistical significance for a true difference.

One set of the statistical analyses should use a discrete outcome variable (presence or absence of disease). Here either a logistic regression or a log-linear analysis can be used to determine relationships between exposure and disease. When some or all of the independent variables are continuous, the logistic regression should be the method of choice. When all variables are categorical either technique can be used, although the log-linear anlaysis is more appropriate for studying general relations among all the

variables. Any factors found to be important in the study of the comparability of the two cohorts can be forced into the equations. The others can be entered or deleted in a stepwise fashion. This method should point out which variables are most strongly associated with disease and keeps the set of variables used as concise as possible. While life table methods are commonly used in longitudinal studies, they were designed for, and are appropriate to, situations in which the outcome variable is common. The majority of outcome variables in this study are too rare for meaningful use of life table techniques. If there is interest in some fairly common outcome such as rate of divorce post-discharge, for example, life table analyses could be useful.

Much of the laboratory data will provide continuous variables which can be studied for differences between the cohorts. For these variables many classical statistical procedures are available including simple t-tests and their non-parametric analogues as well as multivariate tests for studying syndromes rather than single outcomes. Other techniques that can be used to study interrelationships among variables include factor analysis and principal components analysis. These can be used to describe the relationships and to avoid multicollinearity problems.

Comparison of laboratory test results may indicate early changes which have not yet been expressed as clinically definable disease. Parameters which can be used to estimate differences in the mental well being of the two cohorts include comparisons of the scores on the psychological scales, the results of the perception of general health questionnaire and comparison of the current occupational status of members of the two cohorts.

Significant results found in any of the preceeding analyses should be checked by closely examining the univariate results and by determining whether the effect exists in subgroups of the samples. Final presentation of the data should include explanations understandable at different levels of statistical sophistication.

f. Estimated Sensitivity of the Study

Finally, the level of probability of observed differences should be noted. For those conditions for which a difference was noted but which did not reach statistical significance the probability of being able to find a difference, given the prevalence of the disease or condition and the sample size of the population (taking into consideration age, etc.) should be made. All reporting of levels of significance should take into consideration the effect of multiple comparisons on the same populations.

12. Sample size

Although the actual available number of subjects for the two exposure cohorts cannot be determined until the work on the exposure likelihood index can be completed, the sample size requirements for various possible outcomes can be estimated and an optimal sample size chosen. Figures 3 and 4 have been drawn to indicate needed sample sizes to distinguish between two proportions P_1 (for low exposure) and P_2 (for high exposure) with a fixed risk ratio of $P_2/P_1 = 2$ or 3 respectively. (That is, the outcome is twice or three times as common, respectively in one exposure likelihood group than in the other.) These ratios were chosen to be representative of the lower levels of risk which might be seen, and therefore, to represent the most conservative sample size estimates. We feel that, given the potential for misclassification in this study, risk ratios of less than 2 should not be considered. Figures 1 and 2 also utilize a fixed alpha of 0.01 (probability of a type I error) and a one-sided test of $Ho: P_1 = P_2$ with $n_1 = n_2 = n$. The horizontal axis of each graph represents the P_1 or incidence expected in the low exposure group while the vertical axis represents the sample size needed for each group. Each line in the graphs represents a different level of beta, the probability of a type II error. In other words, each line of Figure 3, for example, gives the needed sample size for a given beta for an alpha = 0.01 and a risk ratio of 2. Figure 4 gives the sample sizes for a risk ratio of 3.

We chose the alpha level of 0.01 because of the potential expense of the study and because the seriousness of the questions to be answered dictate a high degree of certainty before results are declared significant. The sample size was computed using the arc-sin transformation for variance stabilization.

$$n = \frac{2\,(Z_{1-\beta} + Z_{1-\alpha})^2}{(2\arcsin\sqrt{P_1} - 2\arcsin\sqrt{P_2})^2}$$

Lemeshow, Hosmer and Stewart (17) have shown that the above sample size formula provides a close approximation to the exact results for very small proportions although it is known to underestimate n somewhat for larger proportions. The sample sizes given in Figures 3 and 4 are those needed for a test of equality of proportions when a simple random sample is taken from each group. For $P_1 = 0.1$ the necessary sample size to detect a doubling in the risk ($P_2/P_1 = 2$) with 95% power is less than 400 in each group (for tripling, less than 120). Hence, the plots do not extend beyond 0.1 on the horizontal axis.

Using the incidence of an outcome variable of interest one can read from the graph the necessary sample size for a desired level of beta. For instance, if one were interested in a comparison of total mortality, which in the general population represents a level of somewhat less than 1%, to detect a doubling ($P_2/P_1 = 2$) of total mortality with a beta of 0.05 (or a power of 95%) one would need approximately 4,500 subjects in each group. If on the other hand one were interested in a cancer which might occur at a level of about one in a hundred thousand ($P_2 = 10^{-5}$), a sample size of about 1.5 million per group would be required to detect a tripling ($P_2/P_1 = 3$) of the rate with 95% power.

The examples above are based on a comparison of yearly incidence. In a follow-up study such as this, one can use the cumulative incidence over the follow-up period. Assuming a group of initially 21 year old men followed for about 12 years, one would expect (from U.S. life tables) a cumulative mortality of about 2%. From Figure 3, then, a sample size of about 2,300 would be needed in each group to detect a doubling in risk at the specified levels of alpha and beta. Likewise in this follow-up period the cancer with a yearly incidence of one in a hundred thousand would have a cumulative incidence of a little over one in ten thousand ($P_1 = 10^{-4}$). To detect a tripling of this incidence at the specified alpha and beta, one would need (from Figure 4) about 150,000 veterans per cohort. As a final example, if

one were interested in a disease with a yearly incidence of about one in one thousand, the expected cumulative incidence would be approximately one in a hundred ($P_1 = 10^{-2}$). A sample size of about 4,500 per group would be required to detect a doubling in the rate.

As can be seen, when the graphs are plotted on log-log paper, the lines are "parallel" (have constant vertical distance between them) and almost straight for $P_1 < 0.01$. If other lines are desired, they can be plotted very simply after calculation of 3 or 4 points using the formula given above.

The graphs can also be used to estimate the effect that practical constraints on sample size would have on the power of the study. Using again the example of total yearly mortality, if the available sample size were 2,900 per group instead of 4,500, the power would decrease from 95% to about 80% (the beta would increase from 0.05 to 0.20). Again, if in the case of the cancer the sample size available were 500,000 per group instead of 1.5 million, the power would drop from 95% to 50%.

The effect on power of being forced to accept a smaller sample size than recommended can be summarized in the following table.

TABLE 4

Available Sample Size as a % of recommended	Power
100%	95%
95%	93.9
90	92.5
85	90.9
80	89.0
75	86.7
70	84.0
65	80.9
60	77.3
50	68.5
40	57.3
35	50.9

This table holds for either risk ratios of 2 or 3 and is derived directly from the arcsin formula:

$$f = \left(\frac{Z_{\gamma} + Z_{1-\alpha}}{Z_{1-\beta} + Z_{1-\alpha}} \right)^2$$

where f is the fraction of the recommended sample that is actually available and γ is the resulting power.

These sample size estimates do not take into account non-response and diminution of respondents due to insufficient data, errors in collection, etc. They also do not take into account the use of multivariate analyses. Therefore, they should probably be increased by at least 20% to ensure that the final number of usable participants is sufficient.

Given these sample size considerations, we recommend a sample size of not less than 6,000 per cohort. This cohort size would be sufficient, after losses from the cohort, to detect at the recommended levels of alpha and beta a doubling of the risk of a disease with an expected yearly incidence of one in one thousand in the low exposure cohort. With 6,000 men per group it should be possible to detect a tripling in the total cancer incidence (approximately 30/100,000 yearly incidence, all males, age 20-29) even with some non-ascertainment.

Figure 3. Sample size needed per group, by frequency of outcome, to detect doubling of risk.

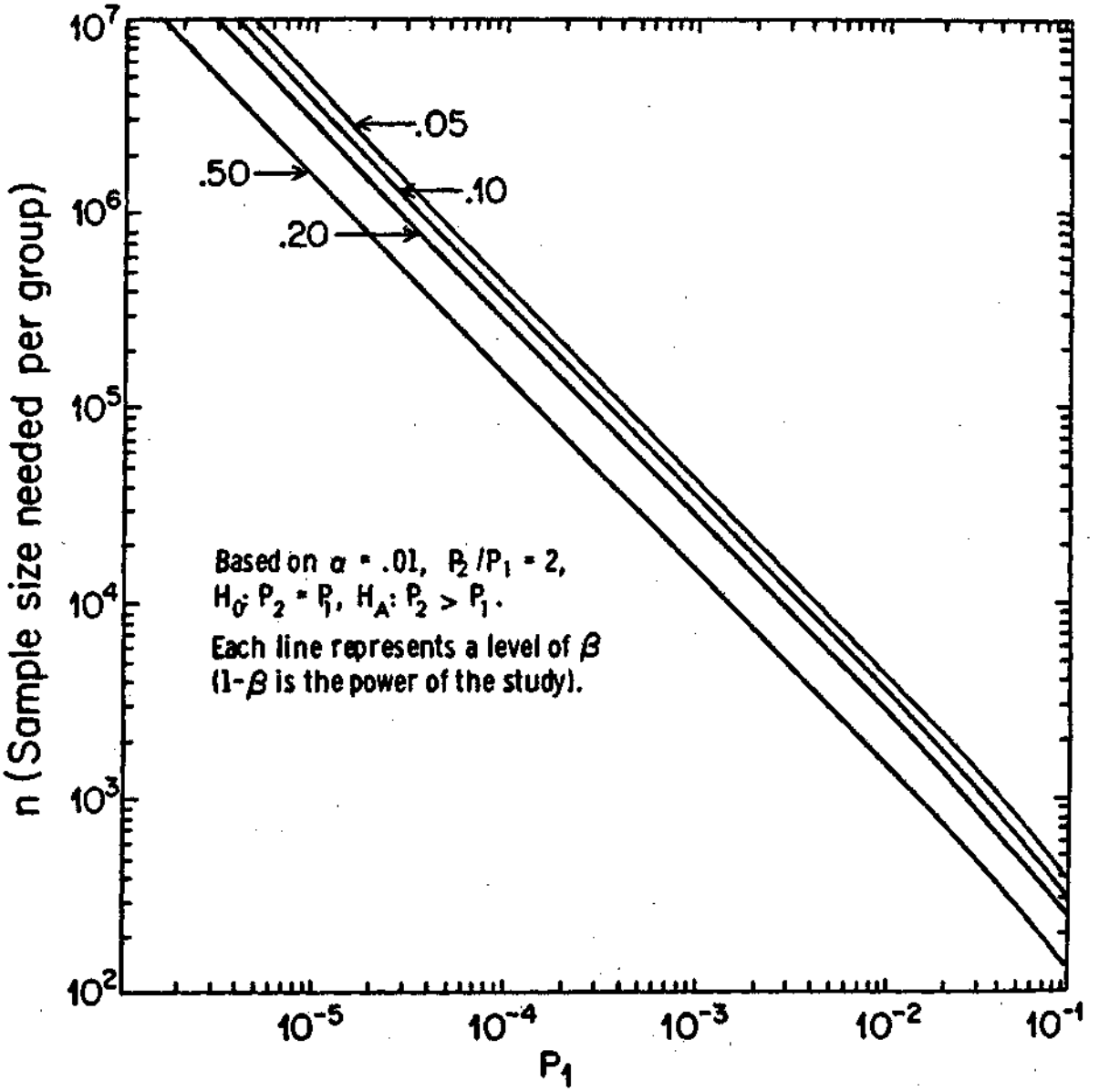
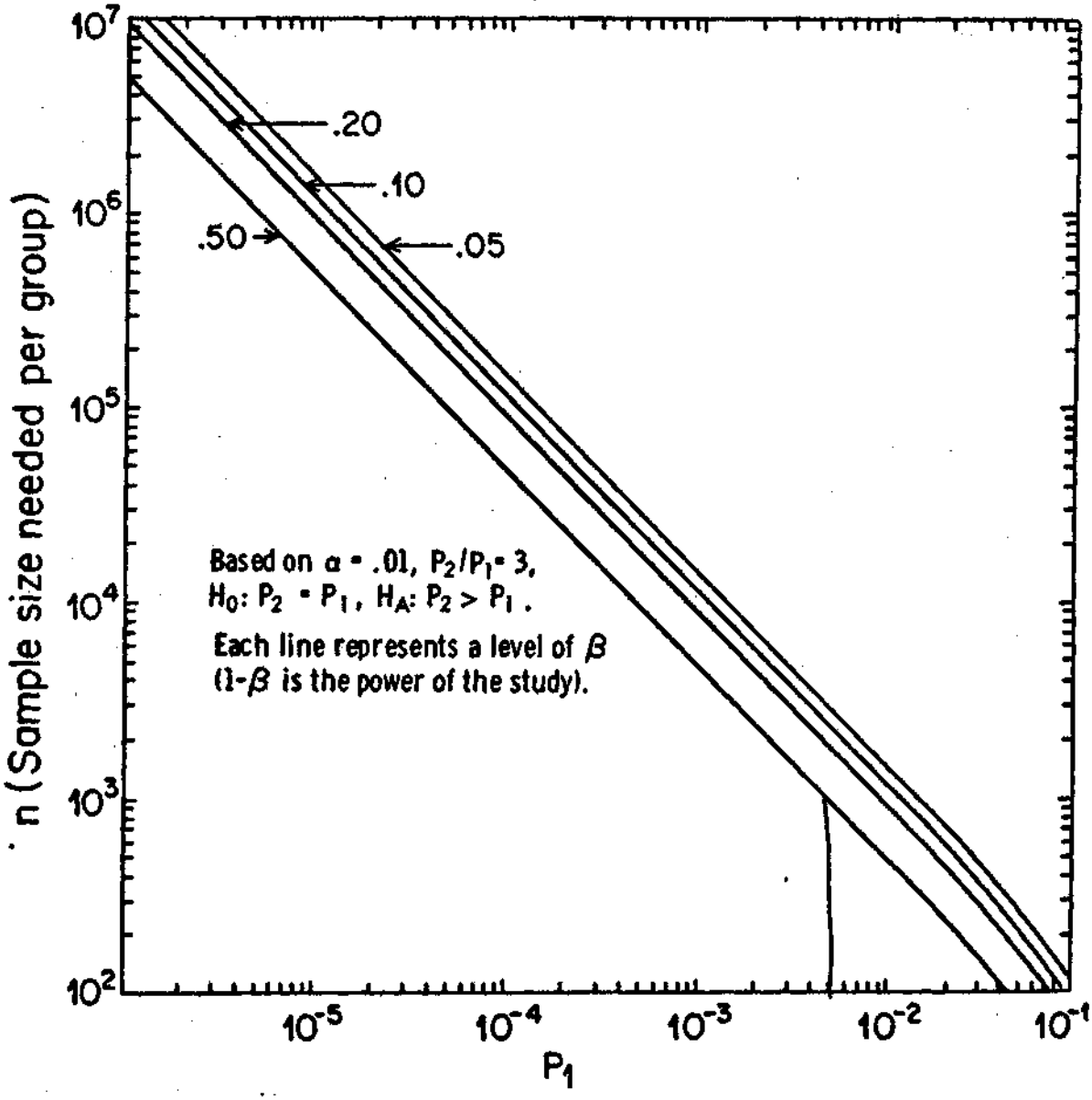


Figure 4. Sample size needed per group, by frequency of outcome, to detect tripling of risk.



13. Organization

Exact specification of the organizational structure of the study requires a decision on whether the Veterans Administration or some independent contractor will conduct the study. The major factors in this decision appear to be greater efficiency and lower cost for a VA run study on the one hand, and serious questions about veteran participation and belief in the ultimate results, if the VA conducts the study, on the other hand. The VA has been accused of having a vested interest in a negative study outcome. Some important data, particularly on veteran participation, can be gathered in the pilot test of the protocol. We believe that the VA hospitals can be utilized as examination centers with an independent coordinating center responsible for the conduct of the study and the data analysis. We outline in this section an organizational structure for this approach. The proposed structure would incorporate the cost savings of a VA study with the generally higher credibility of an independently run study. If, after the pilot test, it appears that the veterans will not accept examinations at VA hospitals, the examination centers will have to be contracted. Probably the best approach would be to identify well established and recognized non-university clinics which could perform the examinations. These centers would have the recognized expertise and may be more likely to participate in a project in which they would have little or

no opportunity for publications than would a university center.

For purposes of cost reduction, advantage should be taken of the large number of regionally located VA hospitals for selection of examination centers. The centers should be chosen to ensure a geographic distribution such that no veteran is required to travel more than 4 hours to reach a center. In addition, as many of the centers as possible should also be university medical center affiliated hospitals. We feel that the Air Force approach of having only one examination center would be impractical for this study because of the expected much larger sample size and the resultant enormous transportation and housing costs.

In each hospital, a minimum staff must be designated to perform all study examination procedures. Designation of a dedicated staff will ensure better standardization of examinations and data collection. The minimum staff must include the following: a physician, a neurologist consultant, a nurse, one or more laboratory technicians capable of performing those tests done at the examining facility and a trained interviewer. Depending on the size of the expected veteran population to be examined at each center, additional staff can be designated to the study as necessary. Back-up staff in case of illness, vacations, etc. should also be designated and trained.

Subject participation in any such study is enhanced by ensuring pleasant surroundings and prompt attention. Therefore, in each center a special staff member must be hired or dedicated totally to the study to serve as an examination coordinator. This individual should be responsible for greeting the veterans, ensuring that they are promptly examined and ensuring that all laboratory procedures are performed in a coordinated and efficient manner. No veteran should be required to wait for any portion of the examination for more than 15 minutes. In smaller centers, this person can also be responsible for collecting, checking and forwarding to the study headquarters all data collection forms. In larger centers an additional staff member would be required for this function.

A coordinating center should be established by contract to a well-respected research organization with proven epidemiolgic expertise included in the permanent staff. This group must have total authority over all study personnel including those in the examination centers. The coordinating group should be headed by an experienced epidemiologist and an experienced manager. At a minimum, this group should also contain: a statistician in charge of data management, an individual in charge of veteran tracing efforts, and an individual in charge of examination standardization procedures. Each of these individuals will

require a support staff. The size of the support staff will depend on the ultimate sample size and other intangibles, such as the difficulty encountered in tracing. These other factors should be identified in the pilot test of the protocol.

The coordinating center should be responsible for all subject identification and tracing. They can delegate to the examining centers the actual contact and scheduling of the individual subjects. The coordinating center should also be responsible for: 1) ensuring proper coordination of the examining centers, 2) ensuring standardization of data collection procedures, 3) collection, coding, cleaning and management of study data, 4) analysis of study data, 5) notification of centers if abnormal examination findings are discovered, and final notification of veterans of appropriate study results.

An independent scientific overview committee might also add to the eventual credibility of the study. This committee could also oversee the conduct of the pilot test. The membership of this committee, if established, should include: at least one eminent epidemiologist, at least one eminent statistician, a physician specialist in physical examination procedures, a specialist in clinical laboratory procedures, a data management expert, and an expert in questionnaire design and administration. The committee should meet on a regular basis with the senior members of

the coordinating center to review progress of the study. Such meetings should be held quarterly at a minimum, and probably more often at the beginning of the study. The operating budget of the oversight committee should be sufficient to allow members to travel as needed to various examining centers or to the coordinating center to review study procedures in progress. Care must be taken to ensure that the oversight committee has sufficient funding to properly serve its function of independently assessing compliance with the protocol.

14. Notification of subjects

We believe that individual subjects should be initially unaware of their exposure status according to the study definition and of the possible anticipated outcomes because of the possibility of conscious or unconscious bias on the part of the participants and/or the interviewers. In addition, the implications of possible exposure will not be understood until the completion of the study and the analysis of study results. We believe, therefore, that notification of the participants of their assumed exposure status should be reserved until the completion of the study. At that time the individuals should be notified of their exposure status and also be given information on the study results and the possible implications of their exposure.

The more immediate question is that of significant illness or abnormality which may be discovered during the examination period and which is unknown to the individual (i.e., is unreported in the medical history). The examining physican should be responsible for notifying the participant of any abnormality found at the time of the examination. This physician should also be responsible for checking all laboratory results performed at the examining hospital, notifying the participants as needed and encouraging appropriate follow-up.

As outlined in the section on data management, the data from each examination (including the centrally performed laboratory analyses which should be reported directly to the coordinating center) should be keypunched, entered into the computer and checked for accuracy and consistency within one month of the time of examination. The data from each individual should then be checked for abnormal findings. Any identified abnormalities which were unreported in the medical history should then be reported immediately to the individual examining center. This would allow the center to follow-up any abnormalities they might have missed or abnormalities found in the centrally done laboratory analyses. The coordinating center responsibility for notification of the examination centers should rest with a designated physician who will review the records of any individual with an identified abnormality. While the examining centers will have the responsibility for the direct contact and follow-up with individual subjects, the coordinating center should be responsible for overseeing the notification to ensure that it is properly accomplished.

15. Pilot testing of protocol

A study of the size, complexity and probable cost of this proposed study should not be done without adequate pilot testing. Pilot testing has several purposes: a) to test the overall feasibility of the study and of the individual components of the study; b) to revise and refine the study procedures so as to maximize the quality of the data to be collected and the efficiency of the study operations; and c) to estimate the costs of the overall study operation and of individual study components including identification of compromises between cost and data quality which may be necessary. Pilot testing should include selection of high and low exposure cohorts and, therefore, should only be conducted following the satifactory development of an exposure likelihood index.

The pilot test should include testing of all forms and procedures necessary for the final study. This can be done on a sample of men identified in the exposure likelihood index. We recommend 200 men from the high likelihood of exposure group and 200 men from the low likelihood of exposure group be examined. This number is not based on considerations of comparison of outcome measures since outcome measures should not be compared in groups in this pilot test. The sample size, however, is adequate for comparison of differences in tracing or participation rates and is large enough to ensure a

reasonable likelihood of identifying major problems which might be encountered, eg, any problem affecting more than about 5% of the subject population.

The 400 individuals should be chosen randomly from the potential subjects in each exposure likelihood group (200 per group) and should then be traced and contacted according to protocol procedures given in sections III B 7 and III B 8. We recommend the simultaneous application of a variety of the most promising tracing procedures, including a search for family members, particularly parents, the use of Veterans Administration records and the IRS records. By such simultaneous application of tracing methods to all pilot test subjects, the procedures with the highest yield and least cost can be identified and the best tracing protocol can be established.

The subjects should be invited to an examination center to undergo all examination procedures as detailed in section III B 5. A single examination center with excellent transportation and nearby housing facilities should be selected. The entire program of staff training can then be developed and pilot tested as well. While the use of a single examination center would have high transportation and housing costs, the concentrated effort on a single center would provide the best test of study procedures without having to deal with intercenter variability.

The data should be recorded on the developed draft study forms and coded and managed according to the procedures recommended in that section. Final coding schemes and computer entry formatting should be completed after examination of the collected data when the range and nature of the responses are known and the final content decided upon. The data analysis should consist of data screening, search for outliers and missing values and appropriate univariate analysis. The cost of each procedure, the frequency of non-traceable individuals, the frequency of nonparticipation and the frequency of missing data or nonreporting for each study variable should be estimated.

Upon completion of this pilot phase, it should be possible to refine the protocol to eliminate collection of data which occurs too infrequently to be of further value and to refine study procedures to account for problems identified in the conduct of the pilot study. In addition, it should be possible to estimate the ultimate cost of the full study.

We recommend that the overall results of the pilot study be reviewed to decide on the merit of continuing with the full study. In particular if the proportion of untraceable individuals is greater than 20% in either cohort, or if there is a difference of more than 10% in the proportion traced in the two cohorts, we recommend that the full study not be done. Likewise if the rate of refusal to participate among veterans is more than 20% of those traced, or there is a differential in refusal rate of greater than 10% between the two cohorts, the study would be unlikely to be successful. These criteria can be applied independently. Overall, a combined non-traceability and refusal rate of greater than 30% or a differential between the groups of greater than 15% (ie, it should be possible to collect data on at least 70% of the members of the cohorts with a spread of, for instance, less than the difference between 70% in one group and 85% in the other group) should be considered criteria for not proceeding with the full study unless a solution to this problem can be identified. Decisions about the cost of the study will depend upon the availability of resources.

16. Timetable

After acceptance of the protocol, selection of the coordinating center, hiring of staff and receipt of security clearances, we estimate the timetable as follows:

a) development of the exposure likelihood index - 12 months

b) selection of cohorts - 6 months

c) pilot test

planning (concurrent with b)

conduct - 3 months

analysis and revision of protocol - 6 months

d) full protocol

selection of examining centers (concurrent with c)

hiring and training staff - 3 months

tracing and recruiting subjects

and conduct of exams - 24 months

analysis - 12 months

This represents a total of 5 1/2 years from acceptance of the protocol to completion of the final analysis. It should be noted that the conduct of the full protocol is expected to take 3 years. The rest of the time will be needed to complete necessary preliminary steps including developing the exposure likelihood index, selecting the cohorts for the study, hiring and training staff, pilot testing the study and revising the protocol as necessary.

17. Future follow-up of subjects

We have not designed a specific protocol for the future follow-up of veterans who participate in this proposed study. A decision on whether further follow-up is warranted should await completion of this proposed study and other studies currently underway. At a minimum we recommend that regular follow-up for mortality be conducted. This could be done fairly inexpensively, although not totally accurately because of exclusions from the system, by a yearly query of the National Death Index. Much additional information could be gained by also obtaining the death certificates so that the distribution of causes of death could be examined.

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