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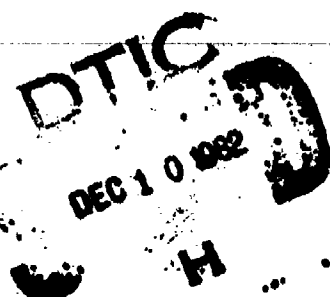
EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDES: STUDY PROTOCOL

George D. Lathrop, Colonel, USAF, MC

William H. Wolfe, Lieutenant Colonel, USAF, MC

Richard A. Albanese, M.D.

Patricia M. Moynahan, Colonel, USAF, NC



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USAF SCHOOL OF AEROSPACE MEDICINE
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas 78235



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NOTICES

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The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.



WILLIAM H. WOLFE, Lt Col, USAF, MC
Project Scientist



GEORGE D. LATHROP, Colonel, USAF, MC
Supervisor



ROY L. DEHART
Colonel, USAF, MC
Commander

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health effects exist and can be attributed to occupational exposure to herbicides. This study uses a matched cohort design in a nonconcurrent prospective setting incorporating mortality, morbidity, and followup studies. Detailed computer searches of Air Force personnel records, with several cross-referencing techniques, have ensured total ascertainment of the RANCH HAND population. The unique circumstances of exposure in this population of 1264 individuals will permit a semiquantitative estimate of exposure. A comparison group will be formed from a population of 23,978 flight crew members and support personnel who were assigned to duty in Southeast Asia (SEA), but were not occupationally exposed to herbicides. These individuals will be matched to RANCH HAND personnel for the variables of age, type of job, and race. Since both the exposed subjects and their selected controls performed similar combat or combat-related jobs, many of the physical and psychophysiologic effects of combat stress and the SEA environment will also be equivalent in the two groups. In the analysis of mortality, each exposed subject and five randomly selected controls will be followed yearly for at least 20 years, constituting a 1:5 mortality design. The first of the mortality controls will be selected and entered into the questionnaire and physical examination phases of the study, producing a 1:1 morbidity design. The initial questionnaire will look backwards in time and will reconstruct occupational, social, and medical data to quantitate morbidity endpoints and confounding factors. All RANCH HAND personnel and their primary controls will be asked to participate in a comprehensive physical examination, with special emphasis being placed on dermatologic, neuropsychiatric, hepatic, immunologic, reproductive, and neoplastic conditions.

The questionnaire will be developed and administered by a civilian opinion research organization of national stature under contract to the U.S. Air Force. In-home, face-to-face interviews will be conducted to maximize data quality. Medical and occupational data will be obtained from the study subjects. Fertility data will be obtained from the subject's spouse and/or former spouses whenever possible, preferably by face-to-face interview. In addition, next-of-kin interviews will be obtained for all study subjects who have died of noncombat-related causes between the time of their assignment to SEA and the initiation of this study. The physical examination will be conducted under Air Force contract at a single center by a civilian medical organization of national stature. Blind assessment protocols and strict quality control measures will be used to avoid bias and limit data variability. Adaptive physical examinations and questionnaires will be developed for use in years 3, 5, 10, 15, and 20 of the followup study. Expected biases and study difficulties include risk-taking behavior bias in the predominantly volunteer RANCH HAND group, response bias, interviewer bias, loss to study bias, and variability of procedures performed.

PREFACE

In 1979 the United States Air Force (USAF) made the commitment to the Congress and the White House to conduct an epidemiologic study of possible health effects resulting from chemical exposure to Air Force personnel who conducted aerial herbicide dissemination missions in Vietnam (Operation RANCH HAND). The purpose of this epidemiologic investigation is to determine whether long-term health effects exist and, if so, whether they can be attributed to occupational exposure to herbicides or their contaminants. The study protocol for this effort incorporates a matched cohort design in a nonconcurrent prospective setting.

The scientific protocol of the Air Force Health Study is presented here and is the result of a maturation process which began in October 1978. At that time, an epidemiologic strategy was developed. After approval of the basic approach was obtained from the USAF Surgeon General in early 1979, full-scale protocol development began in preparation for a series of peer reviews by a variety of expert panels. Throughout this review process, the advice and recommendations of each panel were used to enhance the protocol where appropriate. The following discussion summarizes key recommendations made by each review panel. These reviews were independent of one another, and the approval of one version of the protocol does not imply that those reviewers have approved the protocol in its final form. Although several members of the panels reviewing early protocol versions have received periodic courtesy progress reports, they have not had the opportunity to formally review the final product.

The University of Texas School of Public Health, Houston, Texas, conducted the first review on 8 June 1979. The reviewers stressed the need to insure that the population groups selected for the study were fully ascertained, and that sources of potential bias should be carefully addressed. The advantages of face-to-face interview technique over telephone techniques were discussed as well. On 6 and 7 August 1979, a panel appointed by the USAF Scientific Advisory Board recommended that face-to-face interviews should be used and that the mortality phase of the study be expanded from a 1:1 to a 1:3 design to increase statistical power. Toxicologic aspects of the study and their impact on the scope of the physical examination were extensively discussed. A subcommittee of the Armed Forces Epidemiologic Board conducted a review on 30 and 31 August 1979. The committee members recommended the appointment of an independent monitoring panel to oversee the conduct of the study on a periodic basis. They felt that it was necessary to expand the mortality study to a 1:5 design, with subjects randomly drawn from a 1:10 cohort matrix. Quality control concerns and the advisability of using a single examination center were also recommended. The National Academy of Sciences (NAS) reviewed the protocol on 18 December 1979. The NAS recommendations stressed the need to place increased emphasis on reproductive endpoints, and to expand statistical power calculations, methods of population ascertainment, location, and long-term followup. They reiterated the value of ongoing peer review by a monitoring group. They also strongly encouraged the Air Force to conduct the study by contract to an independent agency to avoid the appearance of conflict of interest. Following the NAS review, additional reviews by the Science Panel of the Agent Orange Working Group and the Advisory Committee on Special

Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants were obtained. A subcommittee of this Advisory Group, chaired by Dr. John Moore, Director of Toxicology and Testing Programs, National Institute of Environmental Health Sciences, was appointed to monitor the study. Reviews by this subcommittee continue on a regular basis.

The edition of the protocol presented in this technical report is the protocol in effect at the time the physical examination phase of the study began in January 1982. Subsequently, circumstances beyond the control of the principal investigators led to some modifications in portions of the design. These modifications are discussed in annexes to the basic protocol (Chapters XVII, XVIII, XIX of this report) and are summarized.

The principal investigators' increasing knowledge of the operational environment of the Vietnam War and the herbicide dissemination programs, and a more complete knowledge of the advantages and limitations of available records, contributed to the refinement of this document. Initially, an individual-specific exposure index or estimate was planned, but these highly specific estimates of exposure were not feasible. Objective data sources were not available to permit development of the index on the individual level, and therefore the use of a more generalized index is required.

The initial ascertainment of the control population was conducted by a computer search of the Air Force personnel records system coupled with a manual search of noncomputerized records. This process resulted in the inadvertent overselection of some comparison individuals who were subsequently found not to meet the criteria for inclusion in the study. These ineligible individuals were removed from the study cohorts, and appropriate subjects were substituted for them. Analysis of the problem revealed that there was true overselection of subjects, and that no eligible subjects had been overlooked. Thus, the statistical and scientific validity of the study has been preserved. As a result of this event, the comparison cohort matrix was reduced from 1:10 to 1:8. This reduction will have minimal consequences, since the 1:5 mortality analytic design and the 1:1 morbidity design are maintained.

The primary focus of this study is the potential effects of herbicide/dioxin exposure on health outcomes. However, the flexibility of the statistical methodology, the comprehensive nature of the data being collected, and the high rates of participation in the questionnaire and examination process will permit the analysis of other factors.

This final protocol represents a synthesis of the comments of all of the peer reviews, coupled with the increasing sophistication of knowledge concerning record sources and operational features of the war. The evolution of this document has occurred over a four-year span of time. This evolutionary process is outlined in the following table. Refinements of concepts and procedures were the only changes made to the study design since November 1979. There have been no substantive changes in study design methods or procedures since that time. Analytic techniques may be further refined to represent state-of-the-art statistical methodology.

PROTOCOL EVOLUTION

<u>Protocol Version</u>	<u>Date</u>	<u>Major Areas of Change</u>
1	6 June 1979	-----
2	10 July 1979	- Expanded discussion of epidemiologic design - Expanded statistical analytic strategy - Consideration of bias sources
3	30 July 1979	- Discussion of exposure index - Development of survival analysis techniques - Expanded discussion of physical examination procedures
4	30 August 1979	- Expanded discussion of exposure concepts - Expansion of mortality study to a 1:3 design - Discussion of compliance factors - Further expansion of physical examination procedures
5	31 October 1979	- Expansion of mortality cohorts to 1:5 - Single center examinations - Discussion of the replacement concept for bias correction
6	28 November 1979	- Expanded exposure index discussion - More detailed discussion of statistical analytic strategy
7	8 October 1980	- Increased emphasis on fertility and reproductive endpoints - Enlarged discussion of the mortality analysis - Enlarged discussion of statistical power - Discussion of Quality Control methods
8	26 November 1980	- Presentation of refined data on study population demographic characteristics

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| 9 | 15 June 1981 | <ul style="list-style-type: none">- Discussion of matching procedures- Consideration of time-in-study effects |
| 10 | September 1981 | <ul style="list-style-type: none">- Expanded discussion of matching procedures and results |
| 11 | 28 January 1982 | <ul style="list-style-type: none">- Refinement of the exposure index- Presentation of modified performance schedules |

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PROJECT RANCH HAND II

EXECUTIVE SUMMARY OF THE PROTOCOL

The Air Force has made the commitment to Congress and to the White House to conduct an epidemiologic study of possible health effects in the Air Force personnel (RANCH HAND) who conducted aerial herbicide missions in Vietnam. The purpose of this investigation is to determine whether long-term health effects exist and can be attributed to occupational exposure to Herbicide Orange. The extensive use of herbicides in Vietnam between 1962 and 1971 was terminated when it became known that TCDD, a contaminant present in 2,4,5-T-containing herbicides, caused congenital abnormalities when administered to pregnant rodents. Subsequent extensive research into the toxicity of TCDD in animals remains equivocal from the point of view of human population risks. Presently, the potential for teratogenicity and carcinogenicity of TCDD seems to be significant, but species specific. The scientific literature on the toxicity of the components of Herbicide Orange reveals that the two main ingredients, 2,4-D and 2,4,5-T, have extremely low toxicity, and are distinctly different in nature than TCDD. TCDD has been shown to be embryotoxic at markedly lower doses in animals. Only recently have comprehensive prospective studies in humans been undertaken. Most previous epidemiologic studies dealing with TCDD exposure in humans have suffered from weakness in design and statistical power. These studies have only validated a link between TCDD exposure and the subsequent development of chloracne. However, the public's perception of the toxicity of Herbicide Orange/TCDD is generally different from that of the scientific community. A review of veteran inquiries submitted to the Veterans Administration reveals an awesome spectrum of alleged symptoms and diseases.

This study uses a matched cohort design in a nonconcurrent prospective setting incorporating mortality, morbidity, and followup studies. Detailed computer searches of Air Force personnel records, with several cross-referencing techniques, have ensured total ascertainment of the RANCH HAND population. The unique circumstances of exposure in this population of 1264 individuals will permit a semi-quantitative estimate of exposure. Specifically, since there was a documented higher concentration of TCDD contamination prior to 1965, this factor will be incorporated in the development of an exposure index. A control group will be formed from a population of 23,978 C-130 crewmembers and support personnel who were assigned to duty in Southeast Asia (SEA), but were not occupationally exposed to herbicides. Control individuals will be matched to RANCH HAND personnel for the variables of age, type of job, and race. Since both the exposed subjects and their selected controls performed similar combat or combat-related jobs, many of the physical and psycho-physiologic effects of combat stress and the SEA environment will also be equivalent in the two groups. Ten statistically equivalent matches for each exposed subject will form the control set for each exposed subject. In the analysis of mortality, each exposed subject and a 50% random selection from each control set will be followed yearly for at least 20 years, constituting a 1:5 mortality design. The first of the randomized mortality controls will be selected and entered into the questionnaire and physical examination

phases of the study, producing a 1:1 morbidity design. The initial questionnaire will look backwards in time and will reconstruct occupational, social, and medical data to quantitate morbidity endpoints and confounding factors. Subsequent questionnaires and physical examinations will constitute a followup morbidity study of living exposed subjects and suitable living controls. In this followup phase, primary controls who are noncompliant will be replaced by another suitable control from the control set so that both statistical power and loss to study bias in the followup study may be improved. Controls dying after the initiation of the followup will not be replaced. All RANCH HAND personnel and their primary controls will be asked to complete a questionnaire and participate in a comprehensive physical examination, with special emphasis being placed on dermatologic, neuropsychiatric, hepatic, immunologic, reproductive, and neoplastic conditions.

The questionnaire will be developed and administered by a civilian opinion research organization of national stature under contract to the U.S. Air Force. In-home, face-to-face interviews will be conducted to maximize data quality; however, noncompliant individuals will be requested to participate in a shortened telephone interview. Medical and occupational data will be obtained from the study subjects. Fertility data will be obtained from the subject's spouse and/or former spouses whenever possible, preferably by face-to-face interview. In addition, next-of-kin interviews will be obtained for all study subjects who have died of non-combat-related causes between the time of their assignment to SEA and the initiation of this study. The physical examinations will be conducted under Air Force contract at a single center by a civilian medical organization of national stature. Blind assessment protocols and strict quality control measures will be used to avoid bias and limit data variability. A \$100 per day stipend will be paid to all eligible subjects to maximize participation in the study. Adaptive physical examinations and questionnaires will be developed for use in years 3, 5, 10, 15, and 20 of the followup study. Expected biases and study difficulties include risk-taking behavior bias in the predominantly volunteer RANCH HAND group, response bias, interviewer bias, loss to study bias, and variability of procedures performed.

Since this study is dealing with nonspecific clinical endpoints, identification or elucidation of a disease state or syndrome by statistical methodology is a prime thrust of the investigation. Inferences about a disease state will be developed by identifying symptom complexes or physical findings which in themselves may represent disease. By comparison of symptoms, signs, and laboratory tests within and between groups, a logical decision-making scheme can be utilized to calculate relative risks from baseline data. If appropriate, these results will be used to sharpen adaptive approaches in the followup study. By the use of combinational and correlational analysis, statements about the probability of a disease state, a subclinical state, and/or over-reporting bias will be attempted. In addition, the application of regression techniques to a normalized exposure index among exposed individuals exhibiting symptoms and/or signs will also assist in the clarification of a disease state or syndrome. Mortality data will be analyzed using several different approaches, including age and age-disease specific rates, standardized mortality rates, and modified life table approaches, as well as more sophisticated logistic and multiplicative models. Analysis of questionnaire and

physical examination data will utilize log-linear models for dichotomous or polytomous data to verify the appropriateness of the standard statistical methodologies (e.g., McNemar's test for dichotomous rates). Continuous variables will undergo covariance analysis to remove noncontrolled effects, followed by the use of a paired difference statistic. Some data will naturally fall into groups or batteries (e.g., fertility/reproduction, liver function tests); in which case, group scoring techniques will be used as appropriate.

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PROJECT RANCH HAND II
EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS
IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDE ORANGE

MATCHED COHORT DESIGN

I. Purpose of the Investigation

The purpose of this epidemiologic investigation is to determine whether long-term health effects exist and can be attributed to occupational exposure to Herbicide Orange.

II. Synopsis of Background

A. The USAF Commitment

Since 1978 news media presentations have focused attention on possible adverse health effects in former military personnel, allegedly due to Herbicide Orange [a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxy-acetic acid (2,4,5-T)] which was used as a defoliant during the Vietnam Conflict. Other herbicides containing 2,4,5-T were also used extensively, and as commonly used by the news media, the term "Herbicide Orange" refers to all of these 2,4,5-T products. These herbicides were contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Figure A-1, Section XV), and the presence of this toxin is the basis for much of the concern over exposure to these defoliants. Claims for compensation have been filed against the Veterans Administration (VA), by more than 3,000 veterans. In response to Congress, the General Accounting Office (GAO) investigated the issue and subsequently recommended that the Department of Defense (DOD) conduct a long-term epidemiologic study of the problem. The Department of the Air Force has made a formal commitment to the Congress and the White House to conduct such a study. On 16 September 1980, the White House directed the DOD to initiate the RANCH HAND study with reasonable speed and high quality. This decision was subsequently reaffirmed by the new administration.

B. The Peer Review Process

This protocol has received rigorous peer review. From the outset, the Air Force principal investigators have acknowledged the scientific complexities of the effort and voluntarily sought outside peer review and consultative guidance. The following reviews have been conducted:

<u>Reviewing Agency</u>	<u>Date</u>
University of Texas, School of Public Health	June 1979
Air Force Scientific Advisory Board	August 1979
Armed Forces Epidemiologic Board	August 1979
National Research Council, National Academy of Sciences	December 1979

Members of each independent review agency were provided copies of the protocol and key references in advance of the review. An extensive briefing of the protocol was presented to three of the four agencies. Each review group provided a report of their opinions and recommendations. The Air Force principal investigators responded to reports from the first three peer reviews and indicated concurrence or nonconcurrence with each of the recommendations. Most of

the peer group recommendations were gratefully accepted and incorporated appropriately within the protocol. Because the National Research Council's report cited "major deficiencies in design" and emphasized public credibility issues, the protocol was referred to the Interagency Work Group to Study the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants for an additional scientific review and recommendations to the White House as to whether the Air Force should conduct this study. This review was conducted in June 1980 and resulted in an affirmative recommendation. The White House subsequently directed that the study be formally started.

C. The Military Use of Herbicides

Research and development on phenoxy herbicides began in the early 1940s, when most of the initial phytotoxic screening programs and the development of application technologies were sponsored by the DOD. The herbicide, 2,4,5-T, was first commercially produced in the United States in 1944. During the years from 1961 through 1969, the DOD procured 53 million pounds of this herbicide (approximately 34 percent of the total US production) for use in the Republic of Vietnam (RVN). However, 8.9 million pounds of that amount were not sprayed in Vietnam, but were destroyed by at-sea incineration in 1977. The first sustained DOD operational use of herbicides was initiated during the Vietnam Conflict (Operation RANCH HAND) and the first shipment of herbicides used in RANCH HAND was received at Tan Son Nhut Air Base, (RVN), on 9 January 1962. The use of these compounds was intended to accomplish two objectives: (1) the defoliation of vegetation to improve visibility and thus decrease the risk of ambush, and (2) the destruction of enemy crops.

Four 2,4,5-T-containing herbicides were used by the military during the period 1962-1970. These four included:

(1) Herbicide Purple (used from 1962 through 1964)

n-butyl	2,4-D	50%
n-butyl	2,4,5-T	30%
iso-butyl	2,4,5-T	20%

(2) Herbicide Pink (used from 1962 through 1964)

n-butyl	2,4,5-T	60%
iso-butyl	2,4,5-T	40%

(3) Herbicide Green (used from 1962 through 1964)

n-butyl	2,4,5-T	100%
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(4) Herbicide Orange (used from early 1965 through 15 April 1970)

n-butyl	2,4-D	50%
n-butyl	2,4,5-T	50%

Analyses of archived samples of Herbicide Purple suggest that the mean concentration of TCDD may have been approximately 33 ppm (Range: 17 to 47 ppm TCDD) while archived samples of Herbicide Orange had a mean concentration of approximately 2 ppm (Range: <0.02 to 15 ppm TCDD).

In addition, two other herbicides were widely used in RVN. These were Herbicide Blue, an organic arsenical formulated from the sodium salt of cacodylic acid, and Herbicide White, a water soluble triisopropanolamine salt formulation of 2,4-D and picloram. The amounts of the various herbicides used in RVN from January 1962 through February 1972 are shown in Table 1.

Table 1.

ESTIMATED QUANTITIES OF HERBICIDES AND TCDD
SPRAYED IN RVN, JAN 1962-FEB 1972

<u>CHEMICAL</u>	<u>POUNDS</u>
2,4-D	55,940,150
2,4,5-T	44,232,600
TCDD	368
Picloram	3,041,800
Cacodylic Acid	3,548,710
Herbicide Total	106,763,260

Ninety-six percent of the 2,4,5-T disseminated in RVN was contained in Herbicide Orange; the remaining 4 percent in Herbicides Green, Pink, and Purple. However, Herbicides Green, Pink and Purple contained approximately 40 percent of the estimated amount of TCDD disseminated in RVN. Green, Pink and Purple were sprayed as defoliants on less than 90,000 acres from 1962 through 1964, a period when only a small force of U.S. military personnel were in RVN. Ninety percent of all the Herbicide Orange (containing 38.3 million pounds of 2,4,5-T and 203 lb of TCDD) was used in defoliation operations on 2.9 million acres of inland forests and mangrove forests of RVN.

Most of the herbicide used in RVN was sprayed from aircraft. RANCH HAND aircraft, the C-123, disseminated 88 percent of all herbicide. Helicopters and ground application equipment used by personnel from all branches of the U.S. Armed Forces applied the remaining 12 percent, primarily Herbicide Blue, to maintain visibility around base perimeters.

Concurrent with the change to Herbicide Orange, the scope of aerial use shifted from four aircrews on temporary assignments, to 36 permanently assigned aircrews, and additional support personnel. Following the announcement in October 1969 that the administration of 2,4,5-T to pregnant rodents

caused an increase in the rate of congenital abnormalities, the DOD confined Herbicide Orange spray operations to nonpopulated areas and in April 1970, all uses of the 2,4,5-T containing herbicides were halted. Other non-2,4,5-T herbicides continued to be used until June 1971 and Operation RANCH HAND was officially deactivated in October 1971. In March 1972, all remaining stocks of 2,4,5-T-containing herbicides were removed from RVN, and transported to Johnston Island, Pacific Ocean, for open storage (Project PACER IVY), and eventual incineration at sea in 1977 (Project PACER HO). In 1979, the Environmental Protection Agency (EPA) suspended the use of herbicides containing 2,4,5-T because an epidemiologic study in the United States attributed abortogenic effects to its use.

III. Goals of the Investigation

The health goals of this investigation are: (1) to identify veteran and active duty individuals with adverse health effects (physical and psychological) if any, which are attributable to herbicide exposure, and (2) to identify other individuals at risk of developing future adverse health effects, if such exist.

Spinoffs from the primary health goals are clearly evident. Increasing media emphasis, in tandem with rising veteran concern and Congressional action, have caused numerous governmental agencies to pursue the issue from several scientific perspectives. The RANCH HAND study is an important part of the overall scientific mosaic, but in itself, may not be definitive in answering the herbicide question. Nevertheless, it is clear that data and conclusions arising from this investigation, whether positive, negative, or indeterminant, will be used as a substantive data base upon which government can formulate policy decisions. With numerous individual and class action lawsuits pending, currently totaling in excess of \$44 billion, the primary governmental decision will concern compensation for attributable adverse health. As the award of compensation to any veteran is solely controlled by the Veterans Administration, this Air Force study in no way represents a "conflict" but rather constitutes another reaffirmation that "The Air Force cares for its own."

IV. Synopsis and Discussion of Literature

A. Overview

More than 20,000 scientific articles relating to the phenoxy herbicides have been published since the 1940's. Many of the articles cite herbicide-caused health effects in a variety of animal species, but most early studies used a myriad of herbicide formulations and unknowingly dealt with physically and chemically impure compounds, and the assay technology was far short of today's state-of-the-art. Many human studies have ascribed cause and effect relationships but have suffered from problems of clinical empiricism or questionable methodology. The only consistent chronic clinical finding associated with exposure to 2,4,5-T herbicide and TCDD has been chloracne, recognized by most workers as the herald sign of overexposure to the herbicide and other chloracneigens. It is now recognized that the chloracne was caused by the presence of TCDD rather than 2,4,5-T. Sequelae from chloracne, localized or systemic, appear to be unusual according to the preponderance of the literature. It is appropriate to note that sustained worldwide usage of herbicides for 30 years has not yet evoked a readily identifiable disease state. It is clear from the literature and the usage history of herbicides that if there are significant attributable long-term health effects, they are either reasonably rare, or of such nonspecific commonality that they blend unnoticeably into the symptoms, syndromes, or diseases associated with increasing age or other similar factors.

B. Pharmacokinetics of 2,4-D, 2,4,5-T and TCDD

(1) 2,4-D

The pharmacokinetics of 2,4-D have been well studied in animals. 2,4-D is readily absorbed after oral administration, and is initially distributed in high concentrations to the central nervous system and liver. Eventually, all tissues are involved, with the kidneys accumulating twenty times the concentration of the other tissues. The plasma half-life of 2,4-D is approximately 3 to 12 hours, with elimination from the body through the kidneys at a dose-dependent rate. Generally, high doses or repeated lower doses result in tissue accumulation. The majority of 2,4-D is eliminated unmetabolized; however, esters of 2,4-D have been shown to undergo hydrolysis prior to excretion. Muscle and fat show the lowest accumulation of 2,4-D on repeated exposure, whereas the kidneys and liver show the highest accumulations. Within 24 hours of single-dose administration of 2,4-D, 16.8% was present in the uterus, placenta, fetus and amniotic fluid in gravid rats. In addition, 2,4-D was found in the milk of lactating rats for up to six days following single-dose exposure.

(2) 2,4,5-T

The pharmacokinetics of 2,4,5-T have been well studied in animals. In all animals, 2,4,5-T has been shown to be readily absorbed upon oral administration. However, beyond this point, 2,4,5-T has shown marked variations in its pharmacokinetics depending on the species tested. These differences are thought to be due to variations in species, age, dosage levels, routes of administration

and chemical formulations used in the various studies. Generally, the distribution is ubiquitous throughout the body except in hamsters, which show no placental passage, and in mice, which show placental passage only in late gestation. Clearance from plasma and from the body varies greatly among species with rats showing faster clearance than dogs, mice and man. In addition, this clearance appears to be generally dose-dependent. The biological half-life of 2,4,5-T in rats, as estimated by tissue analyses and urinary clearance at administered dosages of 5 mg/kg, is 4.7 hours. However, at 200 mg/kg, the half-life in rats is prolonged to 25 hours. Excretion of 2,4,5-T is primarily via the kidneys. The elimination of 2,4,5-T at low doses is essentially achieved in an unmetabolized form. However, at higher or more chronic doses, elimination involves the liver in a more active role (i.e. conjugation). Higher doses and repeated lower doses appear to result in accumulation in animal tissues.

(3) Phenoxy Herbicides in Humans

Relatively few studies have dealt with the pharmacokinetics of 2,4-D and 2,4,5-T in humans. Numerous reports of occupational exposures in industry and in commercial and private herbicide applications have supported percutaneous entry as a major route of exposure. Rapid absorption of 2,4-D and 2,4,5-T has been observed after oral administration. The primary mode of excretion of the phenoxy herbicides is via the urine with 74% of 2,4-D and 63%-72% of 2,4,5-T being cleared from the body within the first 96 hours. The majority of the herbicide is unmetabolized prior to excretion and the biological half-life of 2,4-D and 2,4,5-T in humans (as estimated by tissue analyses and urinary excretion) is 33 hours and 18 hours, respectively. Tissue analysis has revealed an ubiquitous distribution of the herbicides after absorption. Limited studies on the accumulation of the phenoxy herbicides following repeated doses suggest that such accumulation in humans is unlikely. This is in contrast to numerous animal studies on 2,4-D and 2,4,5-T which show that such accumulation does occur.

No specific data are available on the odor threshold of Herbicide Orange. Data are available however, on the odor threshold of a butyl ester formulation of 2,4,5-T. The odor threshold was found to be about 0.3 ppb (the taste threshold was 1.3 ppb). A Threshold Limit Value (TLV) of 10 mg/m³ for both 2,4-D or 2,4,5-T has been adopted by the American Conference of Governmental Industrial Hygienists. The TLV is a time-weighted average concentration for a normal 8-hour workday/40-hour workweek to which workers may be repeatedly exposed, day after day, without adverse effect. Analysis of ambient air samples collected adjacent to and downwind from actual deldrumming operations involving Herbicide Orange were at least two orders of magnitude below the TLVs.

(4) TCDD

Information on the absorption, distribution and excretion of TCDD has been mostly derived from animal models. Studies in rats, mice and guinea pigs generally show that intestinal absorption of TCDD is relatively complete, with a large proportion being stored unmetabolized in the liver. The majority of this TCDD is assumed to be localized in the liver microsomes (centrifugation

techniques). Initially, adipose tissue accumulates TCDD, followed later by accumulation in the liver, adrenals, kidneys and lungs. The level of TCDD in the liver and adipose tissue is about ten-fold greater than in other body tissues; however, significant species variability has been observed. The biological half-life of TCDD varies by species, but is reported to range from 12 to 50 days. The major route of excretion is via the feces with urinary excretion occurring at a much reduced rate.

C. Proposed Cellular Mechanisms of Action for TCDD

TCDD has three proposed mechanisms of action by which its variety of effects, both documented and suspected, can be understood. All currently available information in this area is derived from animal, plant, and bacterial models. The few human studies dealing with mechanisms are limited to the clinical manifestation of chloracne.

(1) Microsomal Enzyme Induction

TCDD's ability to induce a variety of microsomal enzymes is well documented. The induction of aryl hydrocarbon hydroxylase, delta-aminolevulinic acid synthetase, and cytochrome P-448/P-450 associated enzymes has been implicated in the development of cutaneous porphyria. The induction of aryl hydrocarbon hydroxylase and other mixed function oxygenases/oxidases has been associated with carcinogenesis and tumorigenesis. In addition, TCDD has been shown to be a possible promoter or cocarcinogen of known carcinogens. In some nonhuman studies, TCDD produced a protective effect against endocrine tumors (e.g., pituitary, uterine, pancreatic, adrenal, and mammary tumors). TCDD's induction of UDP-glucuronyl transferase, an important enzyme in steroid metabolism, may explain this peculiar effect. The induction of DT-diaphorase and lysosomal acid proteinases has been implicated in TCDD's neuropathic effects. These and other biochemical alterations may account for TCDD's clinical manifestation of chloracne resulting from an over production of keratin in the sebaceous ducts.

(2) DNA/TCDD Interaction.

Alterations in the structure and fidelity of transcription of DNA due to TCDD have been indirectly demonstrated. TCDD, because of its planar ring structure, may "intercalate" with DNA causing "frame-shift" mutations in a manner similar to that seen with the acridine family of compounds. A few laboratory studies with bacterial systems (Escherichia coli and Salmonella typhimurium) and one plant system (the African Blood Lily) have implicated TCDD as being capable of producing chromosomal aberrations and perhaps a weak dominant lethal effect. This hypothesized DNA/TCDD interaction could explain the development of chloracne, as well as the suggested mutagenic and carcinogenic effects, if similar mechanisms occur in mammalian species.

(3) Toxicity.

A nonspecific or as yet unspecified toxicity continues to serve as reasonable mechanism for TCDD's hepatic and thymus toxicity. TCDD has been

described by some as "one of the most potent, low molecular weight toxins known", with extremely low concentrations producing severe liver damage and death in various animal studies. The immune suppression effect of TCDD has been shown to result specifically from its T-cell (thymus) toxicity.

If bioaccumulation and persistence of TCDD occur in human adipose tissue, it could be released into the circulation under situations of weight loss (e.g., life style modification, medical indications, or disease). Such hypothesized reemergence of the agent could result in low doses being either detectable and/or toxic at some later point in time. If TCDD's primary toxicity results from low doses (e.g., a mutagenic/carcinogenic effect) rather than high doses (e.g., cellular poisoning and cell death), then the deposition of TCDD in the adipose tissue may have greater significance with respect to delayed effects on the long-term health of the exposed individual. This possibility raises a theoretical dose-response paradox which might "explain" the prevailing preponderance of symptoms in populations which may have been exposed to relatively low doses of TCDD (see Section IV D). However, persistence of TCDD in humans has not been demonstrated. Attempts to measure TCDD in human tissue are limited by technical difficulty in differentiating between the 2,3,7,8 isomer found in 2,4,5-T and the other 21 isomers from non-herbicide sources. There is also no reasonable method to determine whether tissue TCDD is from an RVN exposure, or from a more recent environmental source.

D. Animal Studies

A comparison of animal toxicity studies is difficult due to variations in experimental designs which include differences in (1) the species, age, and sex of animals used; (2) the level, route, and length of exposure to chemicals; (3) the purity of the chemicals used; and (4) the criteria measured and the time sequence of data collection. Animals have shown a wide range of toxic effects, but this range may serve as a guide to anticipate the potential toxic effects in humans following exposure to Herbicide Orange.

A summarization of the literature is presented in Table A-1 of the Appendix, Section XV. It is apparent that the toxic effects of 2,4-D and 2,4,5-T are markedly different from the effects of TCDD. TCDD is approximately 1000 times more toxic in acute studies. In addition, the slower clearance time of TCDD may account for the significantly lower daily doses required to elicit chronic toxicity. A consistent finding in TCDD toxicity is depletion of the lymphoid tissues throughout the host. This is readily characterized by involution of the thymus in all species studied. In relation to the chronic maternal toxic dose, the embryotoxic dose is markedly lower for TCDD than for 2,4-D and 2,4,5-T. Both 2,4,5-T and 2,4-D appear to be very weak teratogens and/or carcinogens at best, but these evaluations are complicated by varying levels of contamination by various dibenzo-p-dioxins. TCDD appears to have significant teratogenic and carcinogenic potentials which appear to be species specific.

The most striking observation noted in the literature is a marked variation in response among species. Examples of these variations are in the areas of acute toxicity (TCDD's LD₅₀ in guinea pigs is 1 µg/kg compared to 1000 µg/kg

in dogs), excretion (2,4,5-T plasma half-life in rats in 4.7 hrs compared to 77 hrs in dogs), and oncogenicity. Even among strains of the same species (rats) variations in oncogenicity were noted following 2,4,5-T exposures. As noted earlier, this high variability between species is an important consideration in the designing of human studies.

A second area of interest noted in the literature is a hypothetical dose-response paradox in nonhuman primates (rhesus monkey) following exposure to TCDD. Animals in a chronic exposure study fed a low level of TCDD in feed [e.g., 50-500 parts per trillion (ppt)] have shown signs of disease only after several months when total TCDD consumption was approximately 1 $\mu\text{g/kg}$ body weight. Unfortunately, animals receiving comparable amounts of TCDD in a single-dose acute toxicity studies (LD_{50} determinations) have not been observed for the emergence of chronic effects. Therefore, it remains unclear whether the toxicity demonstrated in chronic exposure studies is dependent upon repetitive, cumulative exposure or whether similar toxicity would also be demonstrated following an equivalent single dose after a comparable observation period. Much concern has been raised over the potential of 2,4-D, 2,4,5-T or TCDD to induce genetic change in male animals which are subsequently passed on to the progeny of these exposed animals. In a recent experimental study by Lamb, Moore, and Marks, 150 male mice were exposed to various concentrations of the three chemicals in their food for eight weeks. Acute toxicity was evident with all dosages, as animals lost weight and had dose-related liver and thymus abnormalities, but these effects were reversed upon return to a normal diet. These exposures did not result in abnormalities in sperm concentration, motility or morphology. After the exposure period, the mice were mated, and no dose-related differences in mating frequency, fertility or reproductive success were evident between the chemically exposed mice and their 50 nonexposed controls.

E. Case Reports

Much of the medical literature on 2,4-D, 2,4,5-T and TCDD exposures in humans is based on individual case reports following acute exposures. Since most of the patients discussed in these reports were exposed to multiple chemical agents, it is difficult to determine which agents were responsible for specific symptoms. Nevertheless, the general areas of dermatologic and neuropsychiatric disease have been of primary interest in most investigations. Since the neuropsychiatric symptoms of herbicide exposure are numerous and largely subjective in nature, they have been extremely difficult to assess from a clinical standpoint. In addition, hepatic dysfunction, and renal, gastrointestinal and cardiac disturbances have been "linked" to exposures to these chlorophenolic compounds.

(1) 2,4-D

A multitude of symptoms have been attributed to 2,4-D and the ones reported most consistently are listed in the Appendix, Table A-2. Components of some of these selected symptoms/signs are described in Table A-3 of the Appendix. The allergic syndrome, peripheral neuropathy, and hepatic dysfunction are

of particular interest. Other symptoms of acute systemic toxicity occur, but with 2,4-D exposure has been extensively described. It has an early onset, causes prolonged disability of variable degree, and recovery has been incomplete in many cases. Electromyography in some patients has demonstrated denervation, and some studies have detected decreases in nerve conduction velocities. One autopsy study demonstrated a demyelination process within the brain of a 76-year-old male who committed suicide by ingesting 2,4-D in kerosene.

(2) 2,4,5-T/TCDD

The human effects of 2,4,5-T are difficult to evaluate since the chemical is contaminated with TCDD in the manufacturing process. The effects of TCDD itself have been determined from studies of trichlorophenol workers, and from laboratory workers using TCDD. Symptom/sign complexes attributable to exposure to 2,4,5-T and TCDD are listed in Tables A-2 and A-3 of the Appendix. Chloracne usually begins in the zygomatic/temporal region and is often found on and behind the pinna of the ear. This is an oily acne-like skin condition characterized by comedones and inclusion cysts which may result in extensive scarring. In severe cases following heavy exposure, spread of lesions to the throat, back and inguinal areas has been noted. This skin condition is frequently preceded by erythema and blepharoconjunctivitis. Active lesions usually disappear within two years, but have been found 30 years after exposure. Porphyrria cutanea tarda and hypothyroidism have also been linked to 2,4,5-T/TCDD exposure. Other symptoms such as asthenia, liver and renal dysfunction, neuropathy, and gastrointestinal and cardiac disturbances are probably due to mechanisms similar or identical to those of 2,4-D. With the exception of chloracne and possible disorders of porphyrin metabolism, all of these effects have been acute or subacute in nature.

Numerous instances of alleged disease due to 2,4-D/2,4,5-T exposure have been the subject of heavy media attention, particularly an episode of alleged 2,4,5-T exposure in Globe, Arizona, in 1969. Despite extensive scientific review and analysis with negative findings, the Globe incident continues to be cited in news media presentations. An incident in Missouri in 1971 in which six children, two adults and numerous animals were exposed to TCDD-contaminated oil is frequently described as well. Many of the animals died and the humans developed chloracne and other acute toxic effects; however, all humans were healthy after five years of follow-up study. A final prospective assessment of fertility, teratogenesis and carcinogenesis, in these individuals will probably be made in the future.

F. Veteran Concerns

The Veterans Administration provided the USAF with data on 46,771 patients participating in the Herbicide Registry. Numerous media presentations emphasizing both military and civilian herbicide exposures have described a remarkably wide spectrum of health effects being claimed by the veterans. Three compensation claims have been allowed for service-connected acneiform skin lesions (but not chloracne), 16 claims for other skin conditions, and an additional three claims for other diagnoses. A direct causal relationship between a disease and a specific exposure is not necessary to receive compensation.

If the condition is shown to have occurred during active duty or within a reasonable time after separation, it is compensable, regardless of cause. Current Veterans Administration guidelines state that the only chronic residual of defoliant exposure has been chloracne. Table 2 summarizes the descriptive characteristics of 46,771 patients in the VA Herbicide Registry as of 31 August 1980. Table 3 summarizes symptoms from these patients by category.

Table 2

SUMMARY OF DESCRIPTIVE CHARACTERISTICS OF PATIENTS IN
THE VA HERBICIDE REGISTRY, AS OF 10 FEBRUARY 1981

Total Number of Registered Patients: 46,771	
Branch of Service of Registered Patients:	
Army	66.3%
Marine Corps	18.9%
Air Force	7.3%
Navy	5.9%
Other	1.6%

Table 3

VA HERBICIDE REGISTRY SYMPTOM REPORTING

Number of Registered Patients: 46,771			
Number of Symptomatic Patients: 34,145 (73%)			
Mean Number of Symptoms per Symptomatic Patient: 2.6			
<u>Symptom Category</u>	<u>Number of Patients</u>	<u>Percent of Registered Patients</u>	<u>Percent of Symptomatic Patients</u>
Dermatologic	18,675	39.9	54.7
Psychiatric/Psychological	11,745	25.1	34.4
Head	6,021	12.9	17.6
Peripheral Neuropathy	5,729	12.3	16.8
Asthenia	5,637	12.0	16.5
Gastrointestinal	5,454	11.7	16.0
Sexual Dysfunction	2,105	4.5	6.2
Other	20,702	44.3	---
No symptoms	12,626	--	27.0

Study design implications that can be drawn from these data are limited because registered veterans may not be truly representative of the exposed population. The demonstrated lack of an easily identifiable symptom complex on review of the registry data clearly substantiates the need for a comprehensive evaluation of individual patients.

G. Epidemiologic Studies

Epidemiologic studies of occupational groups have validated links between exposure to TCDD and the development of chloracne. Associations between TCDD and psychological abnormalities have also been suggested. A series of studies published from 1978-1980 by Hardell, Sandstrom, Axelson, and others in Sweden evaluated occupational exposure to chlorophenolic compounds in cancer patients. They found an association between cancer and exposure, but were unable to assess causality due to methodological limitations. Preliminary results of a case-control study of soft tissue sarcoma in New Zealand (Smith) did not detect any unusual clustering of occupations among the sarcoma cases.

Tung (1973) reported an abnormal increase in the occurrence of primary carcinoma of the liver in Vietnam (26 cases per year during 1955-1961 versus 144 cases per year during 1962-1968). He attributed the increase to a suspected carcinogenic effect of TCDD. His published study, however, has been criticized for failure to contain sufficient data and descriptions of methodology to verify his conclusions, and the role of aflatoxin as an alternative cause of liver cancer was not addressed. His study is generally considered to be an empiric clinical observation. A study sponsored by the EPA in 1979 in Alsea, Oregon, found a statistically significant increase in spontaneous abortion in areas where 2,4,5-T herbicide was routinely used in reforestation programs. The EPA concluded that "for all its complexity, this analysis is a correlation analysis, and correlation does not necessarily mean causation." Nevertheless, this study was used by the EPA to institute the ban on most uses of 2,4,5-T containing products. This report has been the subject of intense scientific criticism. Differences in the availability of specialty obstetrical care and in the patterns of health care delivery existed between the exposed and control areas; these differences were not taken into consideration by the researchers. Variations in the ascertainment of spontaneous abortions in each of the areas severely limited the validity of the data, and of the conclusions derived from them. A recent study conducted in Australia (1978) was unable to find an association between neural tube birth defects and the use of 2,4,5-T herbicide. A reproductive study of the wives of 370 2,4,5-T/TCDD exposed workers at the Dow Chemical Company in Midland, Michigan was recently completed (Cook and Bodner). No differences in fertility patterns, fetal wastage, or birth defects were detected.

Epidemiologic studies are continuing in Seveso, Italy, where a population of 220,000 was potentially exposed to TCDD following an industrial accident in July 1976. These studies have involved investigations of more than 30,000 children, and detailed clinical examinations of 1,024 persons, including the most severely exposed children and adults. Recent data (Homberger, et al.,

1979) indicated that most cases of chloracne from this incident cleared rapidly. To date, the growth and development of newborn infants and children, immunological response, chromosomal aberrations, the response to the challenges of infectious diseases, and the morbidity and mortality patterns of the study population have not been significantly altered by TCDD exposure. Thirty-eight cases of birth defects were reported in early 1977, approximately 6-8 months after the industrial accident. However, the authors ascribe this increase to an artifact of surveillance. Analysis of surveillance data on the occurrence of spontaneous abortions after July 1976 is compromised by the lack of valid baselines for the pre-accident period. The social pressures operating in the Seveso population prior to the accident fostered underreporting of birth defects, while the atmosphere after the accident made the occurrence of a birth defect more socially acceptable. The post accident congenital malformation rate is not significantly different than the rate in similar areas of Central Europe.

Another progress report on the aftermath of the Seveso accident (Pocchiari, et al. 1979) has revealed: (1) a decrease in the prevalence and severity of chloracne in the exposed population; (2) an increase in clinical and subclinical neurologic disease as demonstrated by delayed peripheral nerve conduction velocities; and (3) increases in the prevalence of hepatomegaly (8%) and alterations in liver function tests, which returned to normal over an 18 month period of follow-up. Thus far, immunologic, cytogenetic, and embryomorphologic analyses have been unable to detect significant differences between exposed and non-exposed individuals.

A 2,4,5-T Dispute Resolution Conference was held in Arlington, Virginia, from 3 to 7 June 1979. Fifty-six recognized experts from the United States and seven foreign nations were actively involved in the deliberations of the conference. Human Exposure, Carcinogenicity/Mutagenicity, and Teratogenicity Working Groups independently reached the conclusions that there was no valid scientific evidence linking fetotoxicity, teratogenicity or carcinogenicity in humans in a cause and effect relationship to 2,4,5-T/TCDD exposures. The Human Exposure Working Group also concluded that there were no epidemiologic data associating TCDD with any long-term health effects in humans other than persistent chloracne. While they did not find evidence of serious long-term health effects, neither could they find strong evidence for lack of effect. Most previous epidemiologic studies have not had sufficient statistical power to detect increased risks of low incidence/prevalence conditions in the observed populations, and the period of observation in many prospective studies has been less than ideal.

Several potentially valuable epidemiologic studies are currently in progress. Two independent and comprehensive studies of workers exposed to TCDD at a Monsanto manufacturing plant in Nitro, West Virginia, are currently being conducted (Mt. Sinai Medical Center, New York, and the Kettering Laboratory, University of Cincinnati, Ohio). These chemical industry workers were exposed over long periods of time, and were previously evaluated in 1953 and 1956, following an industrial accident which occurred in 1949. Zack and Suskind of the Kettering Laboratory have reported a follow-up study of 122 workers, 28 years

after heavy exposures to TCDD. There were 32 deaths in the group, and the relative risks of death were 0.69 for all causes, and 1.0 for malignancy; however, no firm conclusions can be drawn due to the small numbers involved. A Czechoslovakian study involving a 10 year followup of TCDD exposed workers, and a US National Cancer Institute (NCI) mortality study of 4,400 structural pest control workers are also underway. Preliminary results of a larger study of long-term morbidity by Suskind at the Nitro site have failed to reveal significant abnormalities other than persistent mild chloracne and decreased nerve conduction velocities, possibly associated with alcohol intake.

These new studies, and the continuing evaluations of the Seveso, Italy, population, should continue to provide valuable data. The large study groups involved in the Seveso and NCI studies should provide good statistical power, and the Nitro, West Virginia, and Czechoslovakian efforts will evaluate the effects of exposure after prolonged periods of time (10-30 years). The results of these studies should fill major gaps in the knowledge of 2,4,5-T/TCDD epidemiology, and should prove to be useful in evaluating the long-term effects of these compounds on health and reproductive outcomes.

V. Epidemiologic Study Design: Matched Cohort

A. Design Considerations

The goal of this study clearly mandates a comprehensive epidemiologic approach, incorporating mortality, and historical, current, and followup morbidity studies. Exposure to herbicides during the 1962-1971 time period may have initiated long-term health effects that may or may not be progressive. If such effects are detectable by a review of the subject's past medical history, and can be verified, direct links to compensation issues can be made. Current health status, as mirrored by a large number of recent VA claims and inquiries, is of major interest, because such claims and inquiries may indicate medical conditions that might be confirmed by a comprehensive physical examination. If analyses of both mortality and morbidity data yield only indeterminant or weakly suggestive findings, it may be that sufficient time has not yet passed for substantial emergence of longterm health effects. This dictates a requirement for a follow-up element to the study.

Methodological shortcomings are inherent in each element of this comprehensive study. To some extent, the classical deficiencies of each particular epidemiologic approach are compensated by the concurrent use of the other elements. For example, the low chance of identifying a relatively uncommon disease solely by the use of a mortality study is offset by the inclusion of a current morbidity study. The relatively quick feedback that can be attained from current morbidity and mortality studies will serve to better define the follow-up study, and will help to alleviate problems that arise as a result of changes in diagnostic criteria and methods over time. Nevertheless, problems that can affect ascertainment of disease in all phases of the study will remain. Inaccurate patient recall of antecedent events, the distortion of information by knowledge of anticipated symptomatology, and participant or observer knowledge of their exposure status can only be corrected to a limited extent by review of records for symptom validation and "blind" assessment protocols. In addition, fundamental problems dealing with adequate selection of a control group and limiting loss to study can influence any comprehensive epidemiologic investigation. These and other pitfalls in study design will be discussed in more detail in Section VIII.

The management of this project will be conducted through standard Air Force Research and Development procedures, including program monitors at Air Force Headquarters and Air Force Systems Command, and a Program Management office at Brooks AFB, Texas. Contract monitors will insure that all contractual efforts are conducted according to strict quality assurance procedures, and an on-site monitor will insure that the physical examinations are conducted in strict accordance with the study protocol.

Since the study has three elements and confronts a health issue with incompletely specified or uncertain endpoints, strong potential bias, and severe time constraints, the following design represents the best overall framework for achieving validity. The design process is complex and in itself time dependent.

B. Selection and Ascertainment of the Populations for Study

(1) The Exposed Military Groups

(a) Operation RANCH HAND Personnel

Operation RANCH HAND personnel flew C-123 aircraft in RVN during 1962-1971. Data from hand-compiled lists obtained through the RANCH HAND Association (a reunion organization), Air Force personnel records, unit historical records, and actual C-123 flight orders, place the herbicide exposed population at approximately 1264 individuals. Of those personnel confirmed as RANCH HAND participants, 25% are still on active or reserve duty, with the remainder being composed of retired, separated, or deceased persons. To identify all RANCH HAND participants, an indepth search was conducted of all organizational records stored at the Military Records Division, National Personnel Records Center (NPRC), St. Louis, Missouri.

Introductory letters will be sent to the last known address of all identified persons, and nonresponse will be pursued by cross-locator systems available within the government (e.g., Social Security Administration, VA, Internal Revenue Service). Significant efforts will be made to account for at least 99% of the total population (see Figure A-2, Section XV). Because of the limited number of RANCH HAND personnel, no subsampling of the exposed group is planned in any phase of the study. All members will be strongly encouraged to participate in all phases of the investigation.

All RANCH HAND personnel are males currently ranging in age from 30-69 years (mean = 42.4 years). The normal C-123 crew composition was one pilot, one copilot/navigator (both officers), and one spray equipment console operator (enlisted) in the rear of the aircraft. The aircrew officer-enlisted ratio is 2.2:1; however, the inclusion of RANCH HAND support personnel (predominantly enlisted) in the study will make the overall officer-enlisted ratio 1:1.7. Approximately 98% of the officers and 92% of the enlisted men were Caucasian. Attempts have been made to identify all maintenance personnel assigned to the RANCH HAND units. Maintenance of the RANCH HAND aircraft was performed within a step-wise organizational structure. Routine daily maintenance (primary) was conducted by flight line support personnel who were often dedicated exclusively to RANCH HAND operations. More extensive maintenance (secondary) was carried out by consolidated support units at the base level, which were also responsible for non-RANCH HAND C-123s as well. Major aircraft overhauls and modification were conducted by maintenance units at Clark Air Base, Philippines. The maintenance personnel in these centralized units were not directly assigned to RANCH HAND, and their exposures to RANCH HAND C-123 aircraft and herbicide cannot be validated. From 1962 through 1964, the primary flight line maintenance teams were dedicated to RANCH HAND aircraft, and these individuals have been identified by the mechanisms described above. In 1965, flight line maintenance was performed by personnel of the centralized maintenance organization (secondary), and it is not feasible to adequately identify all of these individuals from available records. After 1966, the RANCH HAND organization transferred their

base of operations to a new location, and primary maintenance was once again performed by personnel assigned specifically to RANCH HAND. These individuals have been readily identified. Thus, maintenance personnel directly assigned to RANCH HAND will be included in the study. These complexities are summarized in Table 4.

Table 4
FEASIBILITY OF IDENTIFYING AIRCRAFT MAINTENANCE
PERSONNEL (TOTAL POPULATION) EXPOSED TO HERBICIDE ORANGE

<u>Time</u>	<u>Primary Maint Personnel</u> ¹	<u>Secondary Maint Personnel</u> ²
Jan 1962-Jul 1964	Yes	No
Aug 1964-Dec 1966	Yes/No ³	No
Jan 1967-Oct 1971	Yes	No

¹individual assigned to RH; total number (denominator) known

²individual not assigned specifically to RH, although may have serviced the aircraft; denominator not ascertainable

³other documents permit ascertainment of a portion of this group

Because of the significant combat hazard associated with low, slow flying missions, some early RANCH HAND crewmembers were elite volunteers (see Risk-Taking Bias, Section VIII, C). In fact, RANCH HAND crewmembers comprised one of the most highly decorated units during the RVN Conflict. Anecdotal stories reveal that most crew members were, on occasion, heavily exposed to Herbicide Orange due to normal or combat induced equipment malfunctions within the aircraft. Many former RANCH HAND personnel are expected to be currently employed in the aerospace industry as commercial airline pilots, airline managers, and flight mechanics. RANCH HAND personnel still on active duty are expected to be found in senior management positions.

(b) Alternate Exposed Populations

(1) Introduction

The principal investigators, members of all of the peer review committees, and independent consultants have clearly recognized that the statistical power of this RANCH HAND study is suboptimal for the detection of specific uncommon conditions or diseases. This limitation is inherent because the size of the RANCH HAND population is fixed at approximately 1200 individuals, and it cannot be increased.

A brief review of alternate military populations is in order to highlight the significant advantages of the RANCH HAND population. The desire to achieve more optimal statistical power by merely increasing the size of the population under study must be balanced with a careful analytic process which assesses the exposure level of alternate populations, and categorizes them as either additive or nonadditive to the RANCH HAND study population.

(2) U.S. Army Ground Personnel

Some U.S. Army personnel were undoubtedly exposed to herbicides during their duty in Vietnam; however, the objective ascertainment of exposed individuals is not possible. Any attempts to identify individuals assigned to combat units which may have been exposed would result in an unacceptable degree of misclassification since U.S. Army personnel records do not exist which would allow the accurate identification of soldiers below the battalion level. This lack of denominator data, and the high degree of misclassification in determining the exposure status of Army troops makes this population unsuitable for inclusion in the framework of the RANCH HAND Study.

(3) Ancillary Air Force Groups (Non-RANCH HAND Personnel)

Air Force handlers of herbicide drums in RVN were exposed to herbicides because of drum leakage. As the drum handlers were ad lib participants, no personnel designator was assigned to these individuals, thus prohibiting computer tracking and identification. The size of this population is unknown, but it is expected to be small (less than 200), as the majority of drum handlers are known to have been Vietnamese. Additional groups such as U.S. Army helicopter crews, casual observers (both Army and Air Force), and experimental fighter-bomber personnel who may have occasionally conducted spray operations were also potentially exposed. However, population-at-risk determinations for all of these groups cannot be made, and any identification of individuals exposed in these situations must rely on self-selection or incomplete ascertainment. Also, the selection of suitable control groups for a study of these individuals is difficult if not impossible.

(4) U.S. Marine Corps Troops

On 16 November 1979, the GAO released a report which suggested that a herbicide-exposed population of nearly 22,000 U.S. Marine Corps troops could be identified, and that this identified group would be appropriate to study. Records exist which locate Marine Corps battalion headquarters near the C-123 spray paths. The GAO made several improper assumptions to conclude that all of the identified marines were in fact exposed. Specifically, all battalion troops were assumed to be located at the battalion headquarters. Further, the effect of prevailing winds on the direction of spray drift, and the photodegradation of the chemicals were not considered by the GAO. The National Research Council panel considered the GAO analysis, and proposed a study of 5900 marines who were "near" spray paths on the same day

as the spraying. The "exposed" group was to be contrasted with the mortality experience of 212,000 presumably unexposed controls (also marines). The RANCH HAND study described in this protocol consists of approximately 1200 exposed individuals and 6000 controls for the mortality study phase. Despite the fact that the RANCH HAND Study involves a smaller sample size than the proposed Marine effort, the RANCH HAND Study is more powerful statistically. Specifically, lower exposure to herbicide by a conservative factor of from 1/10 to 1/1000 and misclassification in Marine exposure groups renders the Marine Study far less powerful than the RANCH HAND effort. As described in Section VI, misclassification and decreased exposure are seen to be independent factors additively decrementing Marine Study statistical power. Even when all 21,900 marines within the herbicide spray paths up to 28 days following the spray operations are considered exposed, the RANCH HAND Study is noted to be significantly superior.

(5) Conclusions

The Operation RANCH HAND participants are the most suitable of the military populations to study in evaluating the longterm effects of herbicide/dioxin exposures. The RANCH HAND group had a much higher level of exposure which was sustained over a prolonged period of time. This increased level of exposure implies that RANCH HAND personnel would be more likely to develop more acute and chronic symptoms from the exposure, and would manifest them sooner than the other exposed military personnel. The addition of significantly less exposed and/or misclassified groups to the RANCH HAND population for the attractive purpose of increasing statistical power would constitute an egregious dilutional error.

(2) Control Group (Not exposed to Herbicide Orange)

A review of all specialized flight units present in Southeast Asia during the RVN conflict, reveals clearly that there is no absolutely ideal control group for the RANCH HAND population. C-130 aircrew members and support personnel were selected because of sufficient population size, similar training profiles, and psychologic similarities to the RANCH HAND group.

Total ascertainment of the C-130 population is being conducted by computer and hand selection for specific military flying organizations, and foreign country service, during the interval from 1962 thru 1970. Over 2.3 million personnel records have been reviewed, and the approximate C-130 population size is 23,978 individuals. Aircrew members who flew C-130 aircraft in Southeast Asia during 1962-1970 were selected as controls for the RANCH HAND aircrew population. The C-130 flight-line maintenance population were ascertained from personnel records by similar mechanisms, and served as the specific control population for the RANCH HAND support personnel. The proportions on active duty, and non-active duty status are expected to parallel the patterns in the exposed group.

Another possible control group, the non-RANCH HAND C-123 population, is known to be too small (approximately 3000) to provide adequate sampling flexibility and replacement under the proposed matched variable concept

(see below and Section VI). Also, many of the RANCH HAND aircraft were reconfigured for transport and insecticide missions and thus, the non-RANCH HAND C-123 crews responsible for these other missions may have been exposed to significant Herbicide Orange residue in these aircraft. Therefore, this group may not have been truly unexposed to herbicides, and was discarded as an appropriate control population. Crewmembers of C-7 transport aircraft were also considered as a potential control group; however, because of small sample size (1000-2000) and the fact that they served in RVN only during the post 1967 era, they were also dropped from consideration.

The normal crew composition of a C-130 is three officers and two enlisted personnel. The control group is considered to be "pure" from the standpoint of lack of occupational exposure to herbicide. The entire control group will be considered "nonvolunteer" with respect to abnormally high combat risk. While in general they will possess lifestyle characteristics and socio-economic backgrounds similar to the exposed group, their overall combat morbidity/mortality and the resultant stress influences upon general health may be slightly less than in the exposed group. For those separated and retired C-130 controls, similar proportions to the exposed group are expected to be employed in the aerospace industry. Known and estimated factors of the control and exposed populations are summarized in Table 5.

(3) Matching Procedures and Rationale

Each member of the exposed group has been computer matched to a set of C-130 controls comprised of approximately 10 individuals using three variables. Since the two groups are highly selected and inherently similar with respect to many variables, very close matches are feasible. This epidemiologic design incorporates a matched concept because: (1) a matched cohort design will provide maximum test power throughout the entire study, and (2) statistical intergroup comparisons may be made without normalization by three key variables known to effect symptom frequencies of interest, thus providing greater power for complex statistical testing. It is apparent that following the match, both exposed and control populations will be very nearly identical with respect to the three influencing variables so that a replacement concept is feasible (see F below). In the event that frequent match breaks occur, stratification techniques can be used.

The selection of the control group produces an inherent match for equivalent SEA experience, and additional matching has been conducted for (1) age, by year of birth and closest month possible, (2) Air Force Speciality Code (AFSC) as an absolute match, and (3) race (Caucasian versus non-Caucasian) as an absolute match. Specific rationale for these variables is as follows: (1) the age match controls for the many clinical symptoms and signs associated with advancing age, (2) AFSC controls for officer-enlisted status (as well as crewmember-noncrewmember status), a variable strongly linked to educational background, current socio-economic status, and moderately linked to age (5 year median difference) and socio-economic background, and (3) race controls for differences in chronic disease development, socio-economic background, etc.

Table 5

COMPARISON OF THE STUDY GROUP TO POSSIBLE CONTROL GROUPS BY
KNOWN AND ESTIMATED FACTORS

<u>KNOWN FACTORS</u>	<u>STUDY GROUP</u>	<u>POSSIBLE CONTROL GROUPS</u>		
	<u>RANCH HAND C-123</u>	<u>Non-RANCH HAND C-123</u>	<u>C-7</u>	<u>C-130</u>
POPULATION SIZE	1264	3000	1200	23,978
OFFICER/ENLISTED RATIO	1:1.7	1:2	1:2	1:2
AIRCRAFT FUEL (AV-GAS)	YES (+JP-4)*	YES (+JP-4)*	YES	NO (JP-4 only)
OCCUPATIONAL HERBICIDE EXPOSURE	YES	YES/NO**	NO	NO
<u>ESTIMATED FACTORS</u>				
OCCUPATIONAL INSECTICIDE EXPOSURE	2+	0	0	0
COMBAT HAZARD	4+	3+	3+	2+
RVN-IN COUNTRY ASSIGNMENT	4+	4+	4+	2+

*In 1968, aircraft were modified with a JP-4 booster.

**Contaminated aircraft reconfigured for transport may have resulted in exposure to non-RANCH HAND personnel.

The inherent match for SEA experience controls for combat-induced physiologic, psychophysiologic, and other related morbidity and mortality disorders. Additionally, this inherent match may reflect the effects of alcohol consumption, the use of chemoprophylactic and/or illicit drugs, and the acquisition of tropical diseases associated with life in SEA. The comparisons of the exposed (RANCH HAND) subjects and their selected sets of controls are detailed in Appendix Table A-4. Only 4 of the ten categorical AFSC/case strata had less than ten controls for each exposed subject. The group of Caucasian pilots had a mean of only 9.5 controls per exposed subject, due to the extreme ages of several individuals, and the strata of Black pilots and other Black officers had means of 2.7 and 5.0 controls respectively. However, since there were only seven black officers in the exposed group and only thirty controls, high numbers of tight matches could not be achieved. Black enlisted aircrewmembers had a mean of 9.8 controls each.

(4) Computer Science and Statistical Details of the Matching Process

As described above, the matching for this project has been performed using three variables: occupational category, race and age. Five occupational categories (officer/pilot, officer/navigator, officer/other, enlisted/flight engineer, and enlisted/other) have been used to reflect socioeconomic status and aeronautical rating. The variable of race has been dichotomized into black and non-black. Ten matched controls have been selected for each exposed subject, regardless of current vital status. The computer method applied to select the control subjects is an adaptation of a procedure studied by Raynor and Kupper (Nearest Neighbor Matching on a Continuous Variable, Technical Report, Department of Biostatistics, University of North Carolina, 1979). As the first step, the RANCH HAND and control groups were partitioned into ten strata using the categorical occupational and race variables. The Raynor and Kupper matching procedure was then applied iteratively within each of the strata to match for the continuous variable of age, given in months. The Raynor-Kupper procedure involves the following steps:

STEP #1. The RANCH HAND cohort in a given strata is randomly permuted.

STEP #2. The first RANCH HAND subject in the permuted set is selected for matching.

STEP #3. The closest available control is assigned to the selected RANCH HAND subject using the absolute value of the difference between the months of birth of the RANCH HAND and the control subjects. If the closest available control is further than 60 months from the selected RANCH HAND subject, a blank is assigned. Tied assignments are broken randomly.

STEP #4. Step #3 is repeated for all RANCH HAND subjects in the strata proceeding down through the permuted set, until the entire RANCH HAND cohort is exhausted.

STEP #5. Steps #1 through #4 are repeated ten times for each RANCH HAND subject to construct a 1:10 study set. At the completion of the matching activity, the RANCH HAND - Control study matrices for each of the ten occupation-race strata can be diagrammatically represented as in Figure #1.

Figure 1. MORTALITY ANALYSIS COHORTS

RANCH HAND COHORT	C ₁ ————— CONTROL COHORTS ————— C ₁₀					
R ₁	C _{1,1}	C _{1,2}	C _{1,3}	C _{1,3}	C _{1,10}	
R ₂	C _{2,1}	C _{2,2}	C _{2,3}	C _{2,4}	C _{2,10}	
R ₃	C _{3,1}	C _{3,2}	C _{3,3}	C _{3,4}	C _{3,10}	
R ₄	C _{4,1}	C _{4,2}	C _{4,3}	C _{4,4}	C _{4,10}	
.	.	.	.	.	.	
.	.	.	.	.	.	
.	.	.	.	.	.	
R _j	C _{1200,1}	C _{1200,2}	C _{1200,3}	C _{1200,4}	C _{1200,10}	

Figure 2. MORTALITY MATRIX

RANCH HAND COHORT	C ₁ ————— CONTROL COHORTS ————— C ₁₀					
R ₁	C _{1,1,m'}	C _{1,2,m'}	...	C _{1,5,m'}	C _{1,6'}	... C _{1,10'}
R _j	C _{j,1,m'}	C _{j,2,m'}	...	C _{j,5,m'}	C _{j,6'}	... C _{j,10'}
.	.	.	.	.	.	.
R ₁₂₀₀	C _{1200,1,m'}	C _{1200,2,m'}	...	C _{1200,5,m'}	C _{1200,6'}	... C _{1200,10'}

In each row of this matrix the controls are ordered from nearest to farthest in terms of age of the matched RANCH HAND person. The next operation defining the control group involved randomization of all of the controls in each row of each stratum matrix to negate the ordering by age. Then, the first five members of each control set for each RANCH HAND person are identified as being subjects in the mortality portion of the study. The resulting occupation-race strata matrices now have the form shown in Figure 2.

In Figure 2, C_{j,k'} or C_{j,k,m'} may be equivalent to any C_{j,k} of Figure 1 due to the randomization process.

Table 6 summarizes the results of the matching process, and Appendix Table A-5 provides a more complete statistical description of the process. In these tables, the age difference between the month of birth of the control and the month of birth of the RANCH HAND person, (counting months from 1900) and the cumulative number of controls and the cumulative percentage with this difference are shown.

Table 6. RESULTS OF THE MATCHING PROCESS (1:10)

<u>Age Difference (in Months)</u>	<u>Cumulative Number of Controls</u>	<u>Cumulative Percent</u>
0	8612	70.6
1	10287	84.3
2	10749	88.1
3	10984	90.1
4	11167	91.6
5	11322	92.8
6	11410	93.5
12	11688	95.8
24	11921	97.7
36	12028	98.6
48	12129	99.4
60	12197	100.0

(5) Study Group Selection Procedures(a) Mortality Analysis

A 50% random sample of each control set will be drawn and used to comprise a 1:5 mortality analysis, as described in section (4). The vital status of each subject in this sample and of all exposed subjects will be ascertained at a minimum frequency of every five years for the 20 year duration of the study. Those individuals dying of combat causes will be excluded from the mortality analysis as it is assumed that combat death is independent of herbicide effect. Further, the known differential combat death rate between the RANCH HAND and control groups can be attributed to the hazardous and unique nature of the RANCH HAND mission. Twenty-two RANCH HAND personnel (15 officers and 7 enlisted) died in combat. Medical record reviews will be accomplished to assess the illness experience of these individuals prior to combat mortality.

(b) Historical Morbidity Study

Retrospective or historical health data will be gathered on each exposed subject and from the first randomly selected mortality control from his set by questionnaire techniques. Living but noncompliant controls in

the historical morbidity study will be replaced by a compliant control selected from the control set. In order to avoid an information gap for data on deceased individuals, surrogate interviews will be obtained from the first order next-of-kin of exposed and control subjects dying of noncombat related causes between the date of their assignment to Southeast Asia and the initiation of this study. Since the validity and accuracy of surrogate derived data may not be equivalent to data obtained directly from living study subjects and their spouses, these data will be subsetting for analysis. All available medical records, (military, VA, and civilian) will be reviewed for all subjects selected for this morbidity analysis.

(c) Prospective Morbidity Study

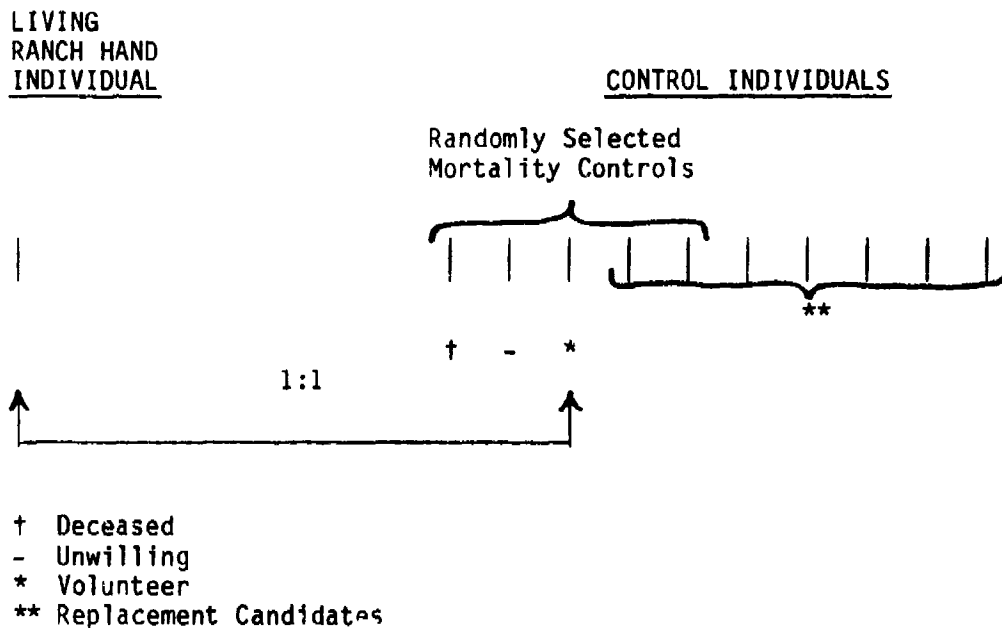
A baseline physical examination and review of systems will be conducted, and a prospective or followup approach will be used to assess the current state of health of study subjects using a series of questionnaires and physical examinations over the next 20 years. Each living exposed subject and the randomly selected primary control will be included in the questionnaire and physical examination phases. In this prospective study of morbidity, primary controls who are deceased, unaccountable or unwilling to participate in the followup studies, will be replaced by a willing subject from the remainder of the control set (Figure 3). The selected control for a RANCH HANDER dying of a noncombat cause will be retained throughout the questionnaire, physical examination, and followup phases of the study. Since the control's vital status and volunteerism should be independent of the matching sequence, many primary controls should enter the study. The remaining members of the control set will be used as replacement candidates for possible use later in the study (see section F below). All replacement controls will be clearly identified for the purposes of subset analysis so that population differences, if any, between the first randomly assigned selectees (noncompliant) and the replacements (compliant) can be assessed. Specific rules and procedures for study entry are found in Table A-6 and Figure A-3 of the Appendix.

(d) The Interrelatedness of the Comparison Groups

It should be clear from the foregoing discussion that the study populations of the mortality, historical morbidity, and prospective followup phases are highly related but different. Once selected, the mortality control cohorts will remain unchanged throughout the 20 years of observation. The population under study in the historical morbidity phase will initially be a randomly selected subset of the mortality comparison group; however, some of these primary controls may be deceased or noncompliant for the voluntary aspects of this phase of the study. In this phase, noncompliant controls will be replaced, but deceased controls will not, as surrogate interviews with the next-of-kin will be used to reconstruct morbidity data. The subsetting and replacement procedures create the difference between the mortality and historical morbidity comparison groups. The population in the prospective morbidity phase is the comparison group from the retrospective phase plus additional replacements for the deceased controls. Thus, it is clear that the comparison groups are slightly different, but they would be identical if no deaths occurred since 1962 and all primary controls were compliant.

Figure 3.

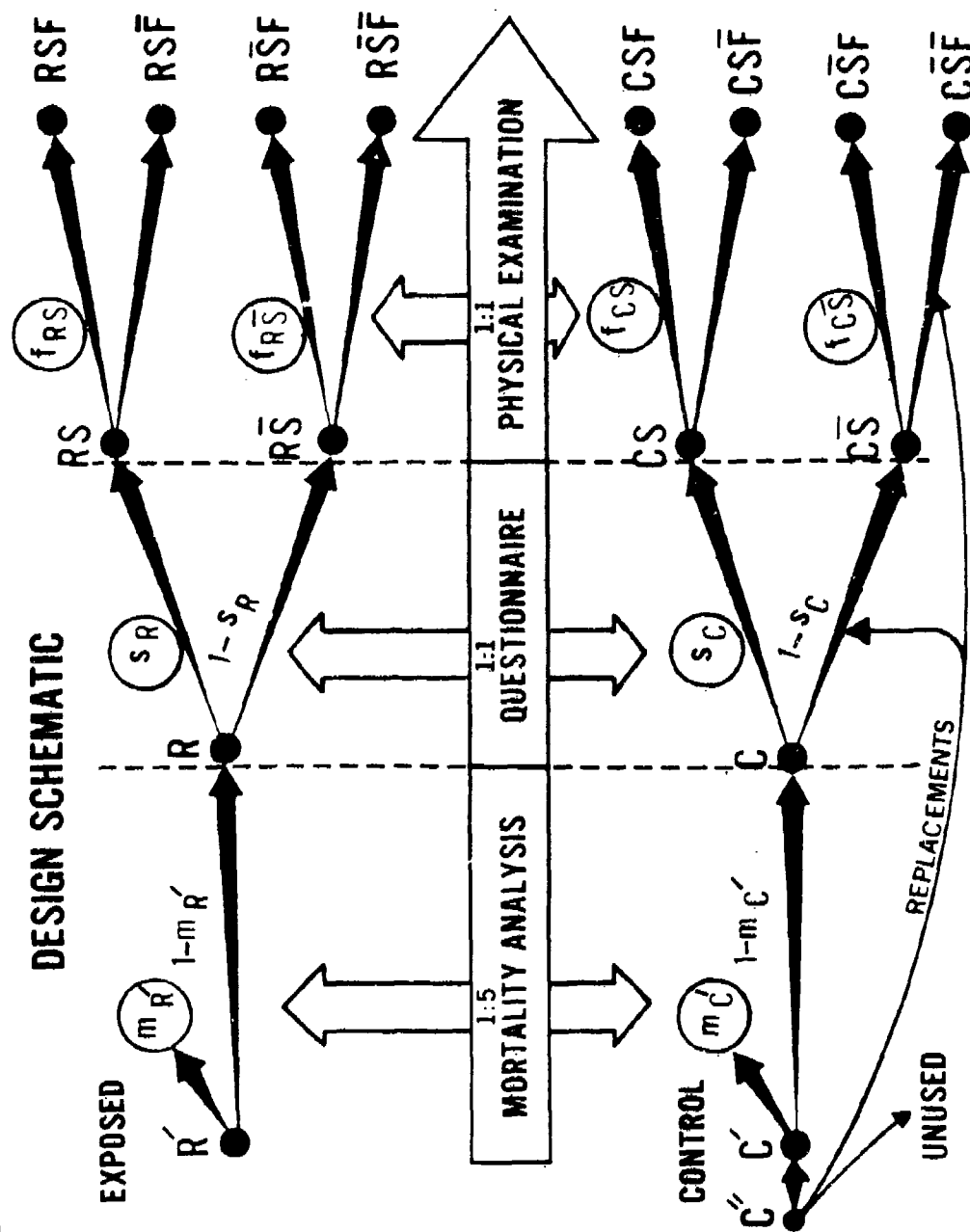
SELECTION PROCEDURE FOR THE QUESTIONNAIRE,
PHYSICAL EXAMINATION, AND FOLLOW-UP STUDY



C. Overview of Statistical Methodology

The design of the study is presented in schematic form in Figure 4. R' refers to RANCH HAND personnel and C" refers to the collection of all possible control individuals. As defined, R' and C" will contain individuals who are deceased of noncombat causes. Combat deaths are excluded from R' and C". Since C" is approximately 20 times larger than R', a randomized subsample C' and C" will be obtained. C' will be constructed from C" by computer selection of the ten matched controls for each exposed study subject. As previously noted, close matches will be made for the variables of age, AFSC, and race. The matched controls will form ten cohorts, C₁ through C₁₀, as shown in Figure 1. A 50% random sample from each of the matched control sets of 10 will be selected for inclusion in the mortality assessment so that a group, C' is obtained that consists of 5 matched controls for each exposed subject. These controls will be designated as initial replacement candidates for the morbidity and follow-up studies. The remaining individuals in the control set will be additional replacement candidates in the event that replacement must occur beyond the members of the mortality set (see Figure 3). C' will be constructed without regard to whether the individual is currently living or dead so that an assessment of noncombat mortality can be accomplished.

FIGURE 4



Referring again to Figure 4, R and C indicate living RANCH HAND members and primary matched controls. If mr' is the proportion of R' found to be deceased, then

$$R = (1 - mr')R'$$

The questionnaire will provide data concerning specific symptoms and other findings in the R and C groups. Thus, various questionnaire finding rates in R, sr , will be calculated and compared with the corresponding rates in C, sc .

The questionnaire will allow allocation of RANCH HAND personnel into those with symptoms on questionnaire, indicated by RS, and those without, $R\bar{S}$. Similarly, the control individuals will be placed into symptomatic, indicated CS, and asymptomatic, $C\bar{S}$ groups.

The physical examination performed on individuals from R and C will allow estimation and comparison of rates of physical findings in these groups. Rates of abnormal physical findings can be symbolically indicated as fr and fc for RANCH HAND and control groups respectively. Comparison of these rates is very important and details will be discussed below.

Let frs be the rate of physical findings among RANCH HAND personnel with findings by questionnaire and let $fr\bar{s}$ be the rate of physical findings among RANCH HAND people with no findings on their questionnaire. For most disease processes it would be expected that frs should be a larger rate than $fr\bar{s}$. If frs is observed to be equal to or less than $fr\bar{s}$, an interpretation of over-reporting may be warranted, although the possibility of subclinical disease is recognized. Rates fcs and $fcs\bar{s}$ will also be estimated, and comparisons between frs , fcs , $fr\bar{s}$ and $fcs\bar{s}$ will be accomplished.

The eight rates mr' , mc' , sr , sc , frs , $fr\bar{s}$, fcs , $fcs\bar{s}$ and their refinements fully characterize this study. As depicted in Figure 4, "vertical comparisons of these rates provide relative risks mr'/mc' , sr/sc , fr/fc , frs/fcs and $fr\bar{s}/fcs\bar{s}$ which are of central importance in defining herbicide effects. "Horizontal comparisons" relate fr to sr , frs to $fr\bar{s}$, fc to sc and fcs to $fcs\bar{s}$. Specifically, the ratio fr/sr is the ratio of physical findings to reported symptoms in the RANCH HAND population. This ratio may be contrasted with the ratio fc/sc and if fr/sr is less than fc/sc over-reporting is suggested. Likewise, if frs is less than $fr\bar{s}$, over-reporting is further suggested. A comparison of $frs/fr\bar{s}$ to $fcs/fcs\bar{s}$ contrasts the odds of findings given symptoms in the RANCH HAND population with the odds of findings given symptoms in the control group. If these odds are lower in the RANCH HAND group, over-reporting is again implied. Further discussion of these rates is presented in Section V.G.

During the questionnaire and physical examination phases of this study, only one of the five randomly selected mortality study controls will be used for each RANCH HAND individual. If this control is unwilling to participate, another mortality study control will be used as indicated in Figures 3

and 7. These replacements will be carefully labelled for purposes of statistical analysis. A detailed discussion of this replacement concept is found in Section VI.

D. Mortality Study

(1) Introduction

The mortality, retrospective morbidity, and follow-up studies are components of a "non-concurrent" prospective study used in the observation of a specially exposed group or industrial population starting from some date in the past. The initial exposures occurred 11-19, years ago and varied in intensity and duration from one RANCH HAND member to another. Access to employment, medical, or other types of records is an obvious requisite for such a study. The classical "case-control", retrospective study is not operative in this protocol due to the lack of defined clinical endpoints. The mortality study will be conducted in two phases; a review of past mortality, and a continuing assessment of the death rate in the exposed and control cohorts over the twenty year duration of the RANCH HAND II project.

Based upon USA vital statistics, 8.6% of the study subjects are expected to have died between completion of their Vietnam tour and initiation of this study. Of these deaths in the control group, approximately 30% should have been due to cardiac causes, 24% to neoplasia, 13% to accidents, 5% to cirrhosis, and 0.1% to leukemia.

(2) Data Collection Methods

The mortality status of the exposed cohort and the randomly selected controls will be ascertained using multiple techniques including: payments of Veterans Administration Death Benefits, Social Security Administration Records, Air Force Accounting and Finance Center wage and retirement payments, and interviews with subjects or their families. Death certificates, autopsy reports, and medical records will be obtained for each deceased subject. The International Classification of Disease, Ninth Revision, 1978, will be used for coding. At the time of the first followup examination, all participants will be asked to allow an autopsy to be performed at government expense at the time of their death, and have the tissues forwarded to the Armed Forces Institute of Pathology, and the results sent to USAFSAM.

(3) Analysis of Mortality Data

(a) Basic analyses

Considering the basic groups R' and C' in Figure 4, individuals will be classified into three categories: alive, dead, or unaccounted. If a large number of individuals in each group are unaccounted for, the study can obviously be severely biased. Thus, significant effort will be expended to reduce the unaccounted category as much as possible. At most, 1 to 3 percent of both groups can be allowed to remain unaccounted, with a 1% rate

being preferred. If for example, the mortality rate in C' is 0.10, then an unaccountability rate of 0.01 could alter the mortality rate by as much as 10%. Whatever the unaccountability rates, the pattern of unaccountability must also be compared between groups R' and C'. For example, the possibility of age differences must be examined, particularly if the unaccountability rates are high. The following paragraphs discuss the analysis of mortality under the assumption that low unaccountability rates have rendered the mortality analysis meaningful.

Multiple mortality assessments will be accomplished during the course of this study, one at the beginning of the study, using available mortality data on the basic mortality cohorts in C' and R' (5:1 ratio), and others using mortality data on R' and all controls used in the study (both C' and replacements) as controls accumulate prospectively. The procedures described here will be used in all of these assessments.

Henceforth, within the protocol, the term "mortality data" does not distinguish between that data collected initially and that data collected in the future.

The mortality data will be analyzed using several different approaches. Crude age-specific death rates will first be calculated and tabulated. Age will be divided into k strata, and person-years will be observed for each strata as will be the number of deaths in each strata. In this manner a tabular display will be developed as shown in Table 7.

Table 7

STRATIFIED FORMAT OF AGE-SPECIFIC DEATH RATES

Age Group	<u>Ranch Hand</u>			<u>Controls</u>		
	<u>Person Years</u>	<u>Deaths</u>	<u>Death Rate</u>	<u>Person Years</u>	<u>Deaths</u>	<u>Death Rate</u>
1	P ₁₁	m ₁₁	r ₁₁	P ₂₁	m ₂₁	r ₂₁
2	P ₁₂	m ₁₂	r ₁₂	P ₂₂	m ₂₂	r ₂₂
3	P ₁₃	m ₁₃	r ₁₃	P ₂₃	m ₂₃	r ₂₃
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
k	P _{1k}	m _{1k}	r _{1k}	P _{2k}	m _{2k}	r _{2k}

Since the death rates r_{1j} and r_{2j} are Poisson variables, they can be contrasted directly. If the relationship of r_{1j} to r_{2j} is found to be consistent between age strata (within statistical variability), a summary mortality index may be calculated. One summary index that will be calculated is the Standardized Mortality Ratio (SMR) which is (Armitage, 1971):

$$SMR = M \times 100$$

$$M = \frac{\sum_{j=1}^k m_{1j}}{\sum_{j=1}^k p_{1j} r_{2j}}$$

"Classical" standardized mortality ratios using national mortality data as the reference will not be calculated for RANCH HAND II due to the effects of the healthy worker phenomenon. The term $\sum m_{1j}$ is the total number of deaths observed in the RANCH HAND group while $\sum p_{1j} r_{2j}$ is the number of deaths that would be expected were the age-specific RANCH HAND death rates the same as the age-specific control death rates. Thus the concern is for an SMR greater than 100%. If a crude death rate for controls, d_c , is calculated as

$$d_c = \frac{\sum_{j=1}^k p_{2j} r_{2j}}{\sum_{j=1}^k p_{2j}}$$

then the standardized crude rate for the RANCH HAND group d_{RH} is

$$d_{RH} = M d_c.$$

An approximate statistical test would regard d_{RH} as a Poisson random variable with mean d_c .

An alternative approach to the provision of a proportionate mortality ratio is that of Breslow and Day (1975). In this treatment, a multiplicative model is employed, for example:

$$\lambda_{ijk} = \theta_i \phi_j \psi_k$$

where λ_{ijk} is the mortality rate, θ_i is the contribution due to population differences (RANCH HAND versus Control), ϕ_j is the contribution due to age

group, and ψ_k is the contribution due to length of time in RVN, etc. The statistical approach here is via maximum likelihood.

Logistic models (Walker and Duncan, 1967) have been extensively studied at USAFSAM for application in cardiovascular disease analysis. These models, in the herbicide context would have the form

$$P = [1 + \exp(\alpha + \beta_1 A + \beta_2 T + \beta_3 R + \beta_4 E + \beta_5 AE + \dots)]^{-1}$$

where

P = probability of death
 A = age in years
 T = length of time in RVN
 R = indicator variable for race
 E = exposure variable

and where $\alpha_i, \beta_i, i=1,2,\dots$ are coefficients to be estimated from the data. Testing for a group difference can be accomplished by estimating β_4 and the interaction coefficients such as β_5 . If all interaction coefficients involving the exposure variable E are zero and E is treated as a 0/1 variable, Cox (1958a, 1958b) has shown that the most powerful test for non-zero β_4 , in the setting of matched pairs, is McNemar's test. This latter test makes full use of the paired design of the study. For McNemar's test, the data are cast into a 2 x 2 table as shown in Table 8. In this table, "a" is the number of pairs in which both members have died, "b" is the number of pairs in which only the RANCH HAND person has died, etc. Using McNemar's test, the test statistic

$$\chi^2 = \frac{|b - c|^2}{b + c}$$

is calculated and referred to the chi-square distribution with one degree of freedom. Cox (1966) and Meittinen (1969) provided extensions of McNemar's test for R controls per exposed (R-to-1 matching). Of course the above analyses will be accomplished considering all deaths, and deaths by specific cause.

As previously discussed, RANCH HAND personnel may be characterized as risk takers. This risk taking behavior may be associated with increased mortality from a variety of causes. On the other hand, herbicide exposure has caused neuropathy in the RANCH HAND personnel, one could anticipate that this disability would increase the probability of accidental death. Therefore,

Table 8
FORMAT OF McNEMAR'S TEST

CONTROLS			
RANCH HAND PERSONNEL	DEAD	ALIVE	TOTAL
Dead	a	b	a+b
Alive	c	d	c+d
Total	a+c	b+d	n

accidental death rates among RANCH HAND participants will be corrected for risk taking. This can be accomplished by including assessment of risk taking behavior in the questionnaire, indepth interview, and psychological evaluation. Both control and RANCH HAND mortality could be corrected using these measures, with the resultant rates being less biased and, therefore, a better indicator of exposed versus control effect.

(b) Mortality analysis without covariates.

The first step in the statistical analysis of survival data is descriptive, i.e., the construction of summary measures which provide a basis for comparing different exposure groups without any allowance for the effects of possibly confounding variables (e.g., age) except perhaps for some limited stratification. Since one must expect many "losses to follow-up", only methods which take full cognizance of this complication will be considered. It should be pointed out that all the methods described below assume independence between censoring (e.g., loss to follow-up) and death or morbid event, although some techniques permit different patterns of censoring in different exposure groups.

The life table method can be adapted to obtain a step-function approximation to survival distributions in the presence of censoring (Chiang, 1968, Gross and Clark, 1975). The failure time distribution is the function $F^0(t)$ which provides the probability of death at or before time t in the study. The Kaplan-Meier estimator of $F^0(t)$ is $\hat{F}^0(t)$ where

$$\hat{F}^0(t) = 1 - \prod_{i \in D(t)} [1 - 1/R(T_i)]$$

In this equation, $D(t)$ is the "death set" at time t , i.e., the set of all indices i of individuals who were observed to fail before time t . $R(T_i)$ is the number of individuals who were at risk just before time T_i , the time of death (or morbid event) of the i th study individual in $D(t)$. A nonparametric approach to testing the equality of survival distributions in a matched

pair study has been developed by Wei (1980). His statistic is a generalization of the Gahan (1965a) statistic. A second test for homogeneity of survival distributions for discretized failure data is the test for marginal homogeneity in a KxK table due to Stuart (1955). Thirdly, the McCullough Model and test may be used on the KxK array to test for marginal homogeneity and stochastic ordering.

(c) Mortality analysis with covariates.

These methods allow adjustment of mortality rates or morbidity rates using covariates such as age, race, length of time in RVN, AFSC, risk taking score, etc. For the purposes of this discussion it will be assumed that the covariables are categorical, that there are only two such covariables and the covariables do not interact in affecting the hazard of death or morbidity. These assumptions can all be relaxed using available methods.

The hazard function $h_i(t)$ for the i th individual in the study is the function which provides the conditional probability of death or morbid event in the time interval $(t, t+dt)$ given his survival up to time t . The function $H_i(t)$ where

$$H_i(t) = \int_0^t h_i(\tau) d\tau$$

is called the cumulative hazard for the i th individual. It is readily shown that the failure time distribution $F_i^0(t)$ is given by:

$$F_i^0(t) = 1 - \exp(-H_i(t))$$

From this last equation it follows that h_i and F^0 are transforms of each other, hence the dependence of F^0 on covariables may be modeled via h_i . This may be accomplished as follows. Let $X_i(t)$ and $Y_i(t)$ denote discrete valued stochastic processes pertaining to the i th individual and describing two covariates of interest (e.g., one may be an exposure variable and the other may be covariate such as age or crew position). A basic model for hazard is:

$$h_i(t) = \exp [\xi X_i(t) + \eta Y_i(t)]$$

where ξ and η are "log-relative risks". This model may be extended to allow for any number of possibly interacting factors. Inference about log-relative risks may be drawn using either an approach derived from D. R. Cox (1972) by E. Peritz and R. Ray (1978) or using an approach described by Frank (1977). Another model, termed the proportional hazards model, is given by

$$h_i(t) = \lambda_0(t) \exp [\beta X_i(t)]$$

The proportional hazards model has been discussed, for the special case that $X_i(t)$ does not change with time, by Cox (1972). A test for the equality of survival distributions in a matched pair study which incorporates the proportional hazard model has been given by Breslow (1975). A test of fit for the proportional hazards model is given by Schoenfeld (1980).

E. Morbidity Study

(1) General Considerations

A vigorous attempt to determine the morbidity experience of all exposed subjects and their primary controls will be undertaken using questionnaires, indepth personal interviews, and physical examinations. A waiver will be requested from the U.S. Attorney General so that medical information collected during the conduct of this study may be exempted from subpoena into Federal Court. Total confidentiality of medical information will be granted to subjects who are not on active duty, and partial confidentiality will be given to active duty subjects with release of information to the DOD only in instances where there is a public safety or national security risk. The schedule and method of contact with the study subjects is depicted in the Appendix Table A-7.

(2) Questionnaire Methods

All living exposed subjects and their primary controls will be offered a comprehensive personal and family health questionnaire administered in the subject's home by a civilian contractor.

In addition to subject interviews, a face-to-face interview will be conducted with the current spouses of the subjects to obtain a more accurate and complete assessment of fertility and reproductive function. Reproductive information that will be collected includes but is not limited to the number of live births, the number of still births, the number of miscarriages, the number of children conceived, the number of abnormal offspring, and the total years of marriage. Previous spouses of divorced or remarried subjects will also be interviewed to obtain similar data. Interviews with the first order next-of-kin of deceased subjects will provide morbidity data on the subject prior to his death. Whenever subjects, their spouses or next-of-kin will not consent to participate in a face-to-face interview, attempts will be made to elicit the information by telephone.

The questionnaire is an important part of this study because non-compliance rates for the physical examination and its face-to-face medical interview are expected to be substantially greater than non-compliance with the initial questionnaire. The questionnaire serves a four-fold purpose: (1) to capture baseline personal and medical data on subjects who might be noncompliant for subsequent physical examinations, (2) to serve as a cross-reference

source for objective data obtained at the time of physical examination, (3) to obtain a targeted medical inventory, independent of the physical examination process, and (4) to obtain health perception data to serve as a foundation for the replacement strategy. As depicted in the Appendix, Figure A-2, only an estimated 40% of the RANCH HAND population will participate in the examination, while at least 65% will respond to the questionnaire. The information collected by questionnaire from these additional 309 individuals and their controls will provide valuable morbidity data which would otherwise be lost. The questionnaire (see Section XI) will emphasize identification data, RVN tour history, dermatologic conditions, neuropsychiatric conditions, fertility aberrations, genetic defects in offspring, sensory defects, and personality factors. A targeted medical inventory will be included in the questionnaire, and will inventory symptoms prior to, during, and after duty in RVN as well as those currently manifested. It will take approximately six months to complete all initial questionnaires on both groups. The questionnaire will be "field-tested" by the contractor on former Air Force personnel with RVN experience. Specific questions on the questionnaire will be directed to verifiable information, wherever possible. Questionnaire development and refinement, including specific response verification procedures have been pursued through civilian contract. Questionnaire data will be cross-linked and integrated with medical record information and physical examination findings. Questionnaire data from individuals not completing all phases of the study will not be discarded, but will be incorporated within the entire data base where statistically appropriate. Each participant will be asked to sign release forms so that all civilian health records, including those of dependents, can be obtained and reviewed as necessary. Attempts will be made to obtain pathological reports and specimens following surgical procedures. Federal health records on all family members on file in the NPRC will be retrieved. For retired members, and separated members with VA privileges, all available VA medical records will be obtained. All retrieved medical records will be reviewed, scored, compared to questionnaire data for reliability, and then be entered into a repository system. Identified participants who are non-responsive to questionnaire will be pursued to determine status, disinterest, moribund state or death, etc. These individuals will be cross-referenced in other federal record systems in an attempt to achieve total ascertainment. Death certificates and autopsy reports will be reviewed on all dead exposed and matched control subjects for the mortality analysis. Birth/death certificates will be sought for all offspring.

(3) Physical Examination

A voluntary comprehensive physical examination will be offered to all individuals in both the exposed and primary control groups within one year of questionnaire administration. The condition for entry into the examination phase of the study will be the completion of the baseline questionnaire. In the event that the primary control does not complete both the questionnaire and the physical examination, a replacement will be selected from the control set [See Figure 3 and Section F(3)]. Statistical testing will be conducted by a variety of techniques on both questionnaire and examination findings. At the time of physical examination, an extensive physical examination, medical

history, and review of symptoms will be conducted. A standardized protocol will be used to insure comparability of data. This will provide cross-reference data to the initial questionnaire and to medical record data, if retrievable. Specific response verification and bias indicator questions will be included in this interview as well.

(a) Examination Parameters

A comprehensive physical examination will be conducted on all willing participants. The examination will be structured as outlined below and in Section XII and will be performed at the earliest practical time following the completion of the questionnaire. The close sequencing of these study components will limit the development of major symptoms in the interval between the questionnaire and the examination. Examinations will be performed under contract at a single civilian medical center having dermatologic, neurologic and electromyogram/ nerve conduction capabilities. Informed consent forms will be obtained for all procedures. Physicians and technicians will handle all participants without a knowledge of exposed or control status, and will conduct the examinations by standardized protocols to minimize variability. Medical students, interns, and residents will not be allowed to perform these examinations, and specialty trained neurologists and dermatologists will perform the appropriate portions of the examination. An onsite monitor will insure that the examination protocol is followed. All laboratory tests will be subject to rigid quality control. Laboratory and physical examination data will be measured on a continuous scale whenever possible in order to improve statistical power in the analysis.

Under special circumstances, additional testing will be accomplished. Karyotyping of the individual and his family members will be considered if clinical history or physical examination findings are suggestive of this need. Most well conducted studies have shown that, when present, chromosomal abnormalities due to TCDD are transient. If on detailed analysis of the baseline examination and questionnaire, reproductive areas are heavily affected, routine karyotyping may be included in the test battery for the followup phases of the study. TCDD analysis on blood and urine will be considered in the future provided that (1) strong cause and effect relationships can be ascribed to Herbicide Orange and (2) high resolution mass spectrometry technology achieves 10 femtogram sensitivity with high isomeric specificity. Serum, urine, and semen specimens will be obtained from all participants, aliquoted, and preserved at -70°C for possible analysis in the future. These serum and/or urine specimens will also be used for analysis of porphyrin metabolites if analytic techniques make this a feasible diagnostic procedure. Extensive immunologic function analyses will be conducted on a randomly selected group of subjects.

Physical examination and laboratory data will be placed in the member's coded master file for detailed cross-analysis to questionnaire data. Information identifiable to the subject will not be released without his consent in accordance with the Privacy Act. However, in accordance with Air Force regulations, active duty flying personnel and active duty air traffic controllers found to have conditions which are disqualifying for flying duty will be temporarily "grounded" pending resolution of the medical condition.

Physical Examination Profile

General Physical Examination	Hemoglobin	CPK
FBS, 2 Hr Post Prandial	Hematocrit	ECG
Urinalysis	White Blood Cell Count	Chest X-Ray
BUN/Creatinine	and Differential	VDRL/FTA
Cholesterol/HDL	Platelet Count	Cortisol Differential
Triglycerides	RBC Indices	Thyroid Profile (RIA)
Serum Protein	Sedimentation Rate	Pulmonary Function
Electrophoresis	Prothrombin Time	Studies
		Blood Alcohol

Dermatologic Examination
Urine Porphyrins
Urine Porphobilinogen
Delta-aminolevulinic Acid

Neuro-Psychiatric Examination
General Neurologic Examination
Psychological Battery:
MMPI
WAIS
WRAT
Halstead-Reitan
Wechsler Memory Scale Subtests
Cornell Index

Nerve Conduction
Velocities

Reproductive Examination
LH, FSH, Testosterone
Semen Analysis

Neoplastic/Hepatic Examination
SGOT
SGPT
GGTP

Alkaline Phosphatase
LDH (Isoenzymes if elevated)
Hepatitis B Antigens/Antibodies
Bilirubin, Total and Direct

Additional Studies (Individuals with abnormal history or examination)
Karyotyping
Hepatitis A Antigens/Antibodies
Anti-Nuclear Antibody
Quantitative Immunoglobulins

Immunoelectrophoresis
Bilateral profile and full-face photographs
Skin Biopsy
Additional Consultations as Required

Immunologic studies (conducted on a randomly selected group of subjects)
Enumeration of B and T Cells
Enumeration of Monocytes

B and T Cell Function

(4) Analysis of Questionnaire and Physical Examination Data

The Questionnaire and Physical Examination will produce data of three types: (1) dichotomous, (2) polytomous and (3) continuous.

Dichotomous (e.g., present/absent) rates will be evaluated using the tools described above for mortality analysis. For example, the questionnaire will provide data concerning the first occurrence of disease states by age, and standardized rates and relative risks may be calculated. The occurrence of such findings can be related to age, time spent in RVN, exposure, and other variables using logistic models followed by McNemar's test where appropriate. These tests will examine the presence or absence of group effect and allow assessment of the statistical significance on non-unity relative risks.

Polytomous findings will occur in both questionnaire and physical examination responses. As an example consider retinal findings categorized into four grades, and studied as a function of age and exposure group as represented in Table 9. In this table the x_{ijk} 's are counts of occurrence. In analyzing tables such as these, techniques as described by Bishop, Fienberg, and Holland (1975) will be used. Specifically, if m_{ijk} is the expected value of x_{ijk} , general log-linear models of the form

$$\begin{aligned} \ln m_{ijk} = & u + u_1(i) + u_2(j) + u_3(k) + u_{12}(ij) \\ & + u_{13}(ik) + u_{23}(jk) + u_{123}(ijk) \end{aligned}$$

will be used, where $u_1(i)$ is the effect of RANCH HAND membership alone on cell frequency, $u_{12}(ij)$ is the effect of an interaction on RANCH HAND membership with retinal grade, etc. This model can work with dichotomous as well as polytomous data. Under appropriate conditions on expected values of entries in Table 9, the pairing in the study design can be used with the data being organized as shown in Table 10. In Table 10, N_{ij} is the number of pairs such that the exposed person has retinal grade i , and the control person has retinal grade j . Appropriate tests for this setting are indicated by Fleiss (1973) and McCullough (1978).

With regard to continuous variables, the intended method follows Carpenter (1977) who found substantial gains in analysis efficiency by matching cases, subsequently employing covariance analysis to remove non-controlled effects. The conditional logistic regression model for relative risk, Holford, White and Kelsey (1978), is also applicable and will be used.

Table 9

FORMAT OF CATEGORICAL REPRESENTATION OF RETINAL CHANGES

Age Category Retinal Category	RANCH HAND PERSONNEL				CONTROLS			
	1	2	3	4	1	2	3	4
1	X_{111}	X_{112}	X_{113}	X_{114}	X_{211}	X_{212}	X_{213}	X_{214}
2	X_{121}	X_{122}	X_{123}	X_{124}	X_{221}	X_{222}	X_{223}	X_{224}
3	X_{131}	X_{132}	X_{133}	X_{134}	X_{231}	X_{232}	X_{233}	X_{234}
4	X_{141}	X_{142}	X_{143}	X_{144}	X_{241}	X_{242}	X_{243}	X_{244}

Table 10

FORMAT OF PAIRING FOR GRADES OF RETINAL FINDINGS

RANCH HAND Grade Control Grade				
	1	2	3	4
1	N_{11}	N_{12}	N_{13}	N_{14}
2	N_{21}	N_{22}	N_{23}	N_{24}
3	N_{31}	N_{32}	N_{33}	N_{34}
4	N_{41}	N_{42}	N_{43}	N_{44}

(5) Analysis of Fertility/Reproduction Data. The herbicides under consideration in this study have been alleged to effect fertility and/or reproductive functioning. An attempt will be made to address these allegations by analyzing at least three primary variables: the total number of conceptions since exposure in RVN, the number of miscarriages in spouses since exposure in RVN and, the number of abnormal offspring since exposure in RVN. The interview with current and former spouses will provide much more accurate information on fertility and reproductive functioning than if similar data were obtained from the male subjects themselves. The study questionnaire will provide the numbers of miscarriages, abnormal offspring and of live births. The sum of the number of miscarriages, still births, and live births will provide an estimate of the total number of conceptions. If differing divorce rates are found in the RANCH HAND and control groups, this may render the average number of years of marriage and the distribution of the years of marriage different in the two groups. This will be investigated and adjusted

for if need be, either by analyzing total number of conceptions divided by (or normalized by) the number of years of marriage, or by using a more detailed covariance analysis. Further, the ratio of the number of miscarriages to adjusted total conceptions will be calculated and compared, as will be the ratio of the number of abnormal births and adjusted total conceptions.

In summary, the following statistics relating to fertility will be calculated and analyzed at the very least:

$$\begin{array}{l} \text{TOTAL} \\ \text{CONCEPTIONS} \end{array} = \# \text{Live Births} + \# \text{Still Births} + \# \text{Miscarriages}$$

$$\begin{array}{l} \text{NORMALIZED} \\ \text{FERTILITY} \\ \text{INDEX} \end{array} = \frac{\text{TOTAL CONCEPTIONS}}{\text{YEARS OF MARRIAGE}}$$

$$\begin{array}{l} \text{MISCARRIAGE} \\ \text{FRACTION} \end{array} = \frac{\# \text{ MISCARRIAGES}}{\text{TOTAL CONCEPTIONS}}$$

$$\begin{array}{l} \text{ABNORMALITY} \\ \text{FRACTION} \end{array} = \frac{\# \text{ ABNORMAL OFFSPRING}}{\text{TOTAL CONCEPTIONS}}$$

F. Follow-up Study

(1) Study Adaptations

Following complete data analysis of the initial mortality and morbidity studies, adaptive or restrictive health surveys will be developed and administered to all follow-up study subjects three, five, ten, fifteen and twenty years after the initial questionnaire. Similarly, a condensed physical examination profile that will achieve adequate sensitivity and specificity for prospective diagnosis will be developed. The adaptive physical examination will be offered to all follow-up participants, and will also be conducted in years three, five, ten, fifteen, and twenty (see Appendix, Table A-5). An interim examination in year three is essential in this study because the age group under study is approaching that portion of the mortality/illness incidence curve with the steepest slope. A lapse of five years between the first two examinations could easily miss significant development of disease in the intervening years. Ample precedent for interim examinations can be found in the Framingham cardiovascular disease study, and in the follow-up evaluation of West Point graduates being conducted by the Air Force.

(2) Entry Criteria

All exposed or control individuals completing the baseline questionnaire and physical examination will be entered into the follow-up; further continuation will depend upon the member's willingness/ability to participate in additional health surveys and condensed examinations. Specific study entry rules are detailed in Table A-6 and Figure A-3 of the Appendix.

(3) Loss to Study; Key Issues

Loss of participants over time adversely affects any epidemiologic study in two ways. As the sizes of the study groups decrease, statistical power also declines, and bias is injected into the study if losses are not randomly distributed in the study populations. It is reasonable to assume that in this study, losses will be non-random with greater non-compliance among individuals who perceive their health as "well," since there is less incentive for this group to continue participation. As shown in Figure 5, such a differential pattern of loss will alter the population, and skew the frequency distribution curve.

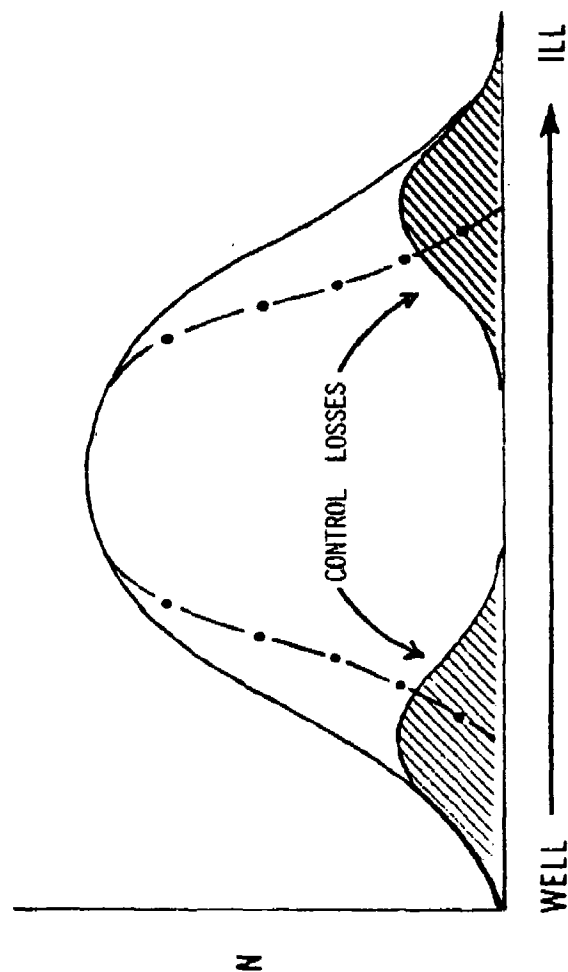
Most previous epidemiologic studies have approached the problem of declining statistical power by beginning the study with multiple controls per exposed subject, and passively allowing attrition to occur throughout the study period. However, this approach does not address the problem of bias. This study will take an active approach to both of these problems by using a replacement concept. As a control is lost to study, a replacement will be chosen from the original set of ten matched controls. The replacement will be selected from the control set, and will have a perception of health similar to that of the lost control (Figure 6). The replacement strategy will maintain statistical power and the integrity of the matched design despite loss to study in the control group, and will correct anticipated bias while minimizing the number of required physical examinations.

At the initiation of the follow-up study, loss of an exposed member will not be cause to cease surveillance of his primary matched control. In the event of a control loss (for reasons other than death), another control from the set will be brought to study (Figure 7), the comprehensive questionnaire will be administered, and a baseline physical examination performed.

If a control is noncompliant for one portion of the study and is replaced by another control, the noncompliant individual will be approached at the time of subsequent questionnaires and examinations, and encouraged to reenter the study. If he reenters, both he and the replacement will be included in the evaluation. Similarly, noncompliant exposed subjects will also be aggressively recruited for all subsequent study phases.

FIGURE 5

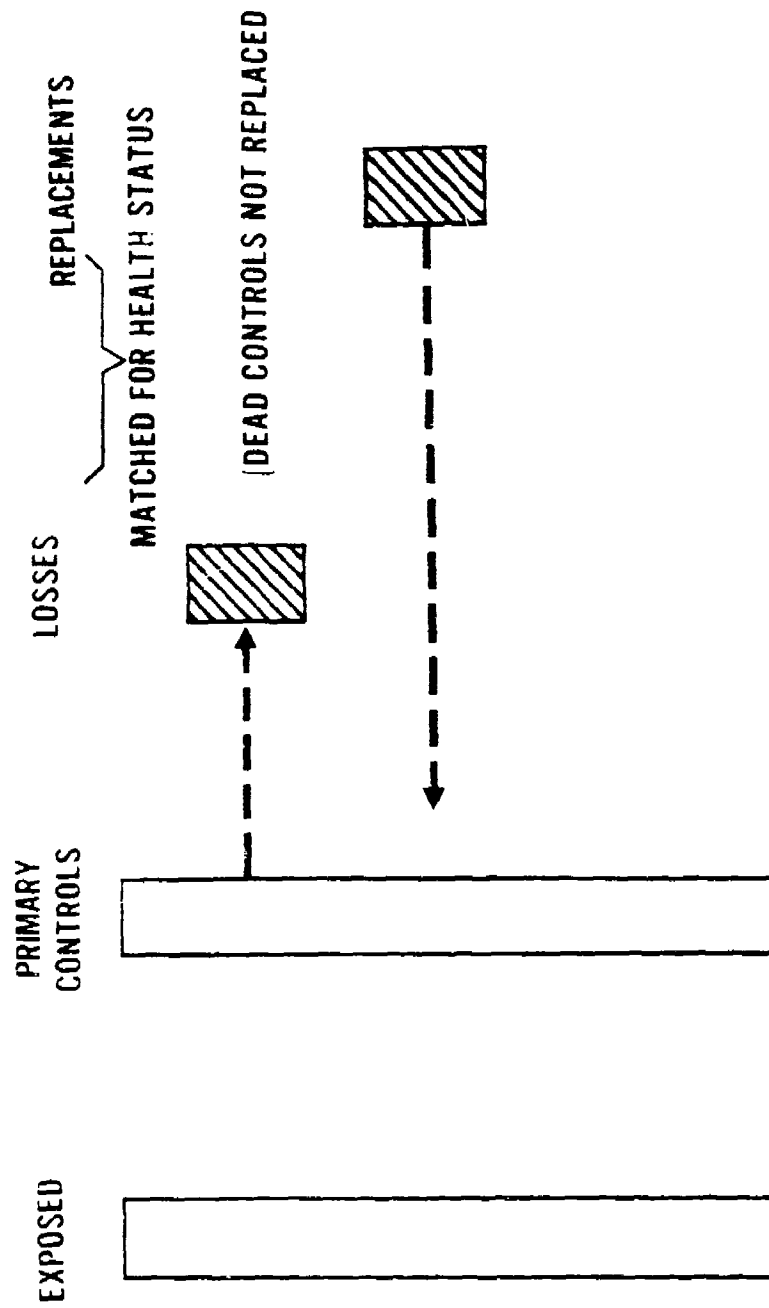
EFFECT OF NON-RANDOM LOSS TO STUDY IN THE CONTROL POPULATION



- IF CONTROL LOSSES ARE ILL, A SPIRIOUS EFFECT IS ATTRIBUTED TO HERBICIDE EXPOSURE.
- IF CONTROL LOSSES ARE WELL, A TRUE/VALID HEALTH EFFECT IS DILUTED.

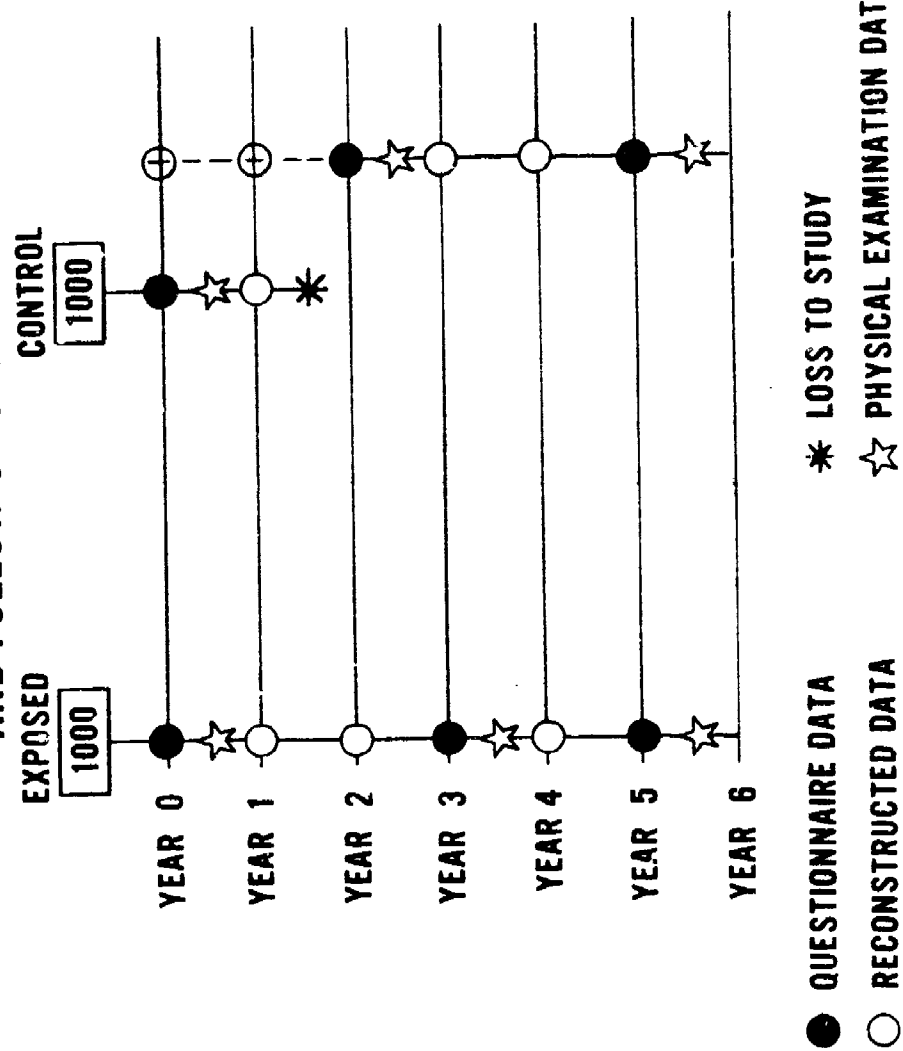
FIGURE 6

THE REPLACEMENT STRATEGY



CONTROL REPLACEMENT FOR THE MORBIDITY AND FOLLOW UP STUDIES

FIGURE 7



For exposed and control individuals who drop out of the study but subsequently re-enter, medical data for the intervening years will be reconstructed from questionnaire and interview responses. IN ALL CASES OF LOSS-TO-STUDY, INTENSIVE EFFORTS WILL BE MADE TO DETERMINE THE SPECIFIC REASONS FOR NON-COMPLIANCE, AND DATA FROM REPLACEMENT CONTROLS WILL BE REVIEWED TO ASSESS COMPARABILITY WITH THE LOST INDIVIDUALS. Medical record reviews of new entrants will continue throughout the follow-up period.

(4) Study Length

The follow-up study is initially planned for 20 consecutive years. Procedures, progress, and interim results of the study will be monitored by an independent scientific review group, responsible to the Office of Science and Technology Policy in the White House.

G. Determination of "Disease"

(1) Introduction

Since this study is dealing with an unknown clinical endpoint with unknown latency, determination of a disease state by statistical methodology is a prime scientific thrust of the investigation. From the literature, chloracne is the only generally accepted chronic disease associated with high exposure to dioxin. The questions of primary interest are: (1) Does a history of chloracne invariably lead to future disease? and (2) In the absence of chloracne, is there emergence of other attributable diseases? Under a broad concept of "spectrum of illness", either or both of these conditions are possible. The clarification of their respective contributions to the natural history of past or of subsequent "disease" is of significant interest.

(2) Discussion

Inferences about a disease state from this study can be derived from several logical approaches. These approaches can be grouped into two categories: (1) those dealing with symptoms which can be used to construct a symptom complex that may represent disease, and (2) those dealing with physical signs which in themselves represent disease. In the former, one can form a subset of individuals that have symptoms (e.g., infertility) and study them during the morbidity and follow-up studies. Focusing on the overall patterns of alleged symptoms and categorizing them into a symptom complex may identify those individuals with a disease syndrome, or those at higher risk of developing disease (e.g., genetic disorders, cancer). In the latter approach, data on abnormal physical signs (e.g., genetic defects in offspring) and laboratory results can be compared between exposed and non-exposed groups in an attempt to again establish the presence or absence of disease. By putting this array of data into a logical decision-making scheme, specific relative risks can be calculated in the follow-up study, and specific response patterns can be inferred as shown in Figure 8.

FIGURE 6

INTERPRETATION OF HORIZONTAL COMPARISONS

OVERT EFFECT	SUBCLINICAL	OVER-REPORTING
$M_R > M_C$	$M_R = M_C$	$M_R = M_C$
$S_R > S_C$	$S_R = S_C$	$S_R > S_C$
$F_R > F_C$	$F_R > F_C$	$F_R = F_C$
$F_{RS} > F_{CS}$	$F_{RS} > F_{CS}$	$F_{RS} < F_{CS}$
$F_{RS} > F_{CS}$	$F_{RS} \approx F_{CS}$	$F_{RS} = F_{CS}$
MORTALITY/SYMPTOM/ SIGN REGRESSION ON EXPOSURE	SIGN REGRESSION ON EXPOSURE	NO REGRESSION ON EXPOSURE SEEN

$$F_R = F_{RS} S_R + F_{RS} (1 - S_R)$$

Again referring to Figure 8, at least three clinical patterns can be defined. These patterns are delineated using relative risks (mr/mc , sr/sc , fr/fc etc., between group or "vertical" comparisons, referencing Figure 4) and using within group ("horizontal" study) comparisons such as regressing symptoms and findings rates against an index of herbicide exposure, and other comparisons. Specifically, an overt clinical effect would be marked by: an increased mortality rate in the RANCH HAND group ($mr > mc$), an increased rate of symptom formation in the RANCH HAND group ($sr > sc$), and an increased rate of objective medical findings in the RANCH HAND group as compared to the control group ($fr > fc$). Further, the occurrence of physical or objective medical findings would consistently relate to symptoms in the overt case (that is, $frs > fcs$ and $fr\bar{s} > fc\bar{s}$), and finally, in the classic instance, mortality, and symptom and sign formation would be seen to be increased with increasing herbicide exposure.

A subclinical pattern is indicated in the central column of Figure 8. In this setting, one expects no statistically significant differences in mortality or symptom reporting between the two groups, exposed versus control. However, one expects a consistent predominance of medical signs in the RANCH HAND group with regression of the signs on increasing herbicide exposure.

A pattern strongly suggesting over-reporting is presented as the right column of Figure 8. In this setting, there is no difference between the groups as regards mortality or medical sign incidence; however, more symptoms are reported by the RANCH HAND group. While in this pattern the RANCH HAND subjects are reporting more symptoms, objective medical finding rates are not consistent with symptom reporting. When no regression of symptoms on exposure level is found, over-reporting is clearly and strongly suggested.

This discussion of response patterns has used regression on an exposure index in a central way. Development of such an index is discussed below. It is noted, however, that a direct index of exposure can be confounded by other factors such as cellular repair mechanisms or bioaccumulation in adipose tissue with release over time upon weight loss. Use of other factors, such as time since exposure, should help to overcome these confounders.

The strength of any inferences made from these analyses is dependent upon the statistical power inherent in the study. In addition, due to the possibility of latency being a factor in this study, a negative analysis at any time within the study does not categorically imply lack of disease, since sufficient time for emergence may not have passed.

H. Exposure Indices

(1) Exposure Concepts

A major concern in conducting this study is the lack of accurate exposure data. Although most personnel assigned to RANCH HAND squadrons were undoubtedly exposed to Herbicide Orange and TCDD, the exposures within the

group must have varied widely. Exposure to herbicides and TCDD by RANCH HAND personnel occurred almost daily. Anecdotal information suggests that many had direct skin contact which was repetitive over a long period of time (one-year tour for most individuals). Further, it is also suggested that most RANCH HAND personnel felt that the herbicides employed in the operations were not toxic to animals and man, and hence, they did not exercise the caution in handling these chemicals that is recommended today.

From a historical review of RANCH HAND operations, it appears most individuals can be classified into one of three groups based on their likely potential for exposure to the herbicides:

- | | |
|---|--------------------|
| (1) Pilots, Co-pilots and Navigators: | low potential |
| (2) Crew Chiefs, Aircraft Mechanic, and
other Support Personnel: | moderate potential |
| (3) Console Operators and Flight Engineers: | high potential |

The "pilot" group received most of their exposure during pre-flight checks as well as during the actual dissemination missions. The crew chief group experienced contact with herbicides during dedrumming and aircraft loading operations, as well as during on-site repair of the aircraft and spray equipment. The console operator group was exposed while supervising the loading of the aircraft, during ground testing of equipment, and by tank leakage during dissemination missions.

The available historical records on Operation RANCH HAND indicate that personnel assigned to the project seldom had a "routine" work schedule or environment, thus complicating estimates of the level of herbicide and dioxin exposure. Since actual exposure data (e.g., mg of herbicide/kg body wt) are not available, an exposure index will be used. The exposure indices will be calculated for each RANCH HAND individual to obtain frequency distribution, and will be calculated by evaluating the known factors that would have influenced exposure. These will include such factors as:

- (1) Date of tour with RANCH HAND in Vietnam.
- (2) Number and lengths of tours in Vietnam with RANCH HAND.
- (3) Number of herbicide dissemination missions (as reflected by flying hours and air medals).
- (4) Herbicides employed (records are available that reflect the amount of each herbicide sprayed each month and year).
- (5) Crew position.
- (6) Routes of exposure (the major route of exposure for most RANCH HAND personnel was probably percutaneous, although exposure through inhalation may have also been significant).

A crude exposure index which is applicable to the entire RANCH HAND cohort is expressed with the following formula:

$$E_i = q_i \times T_i$$

In this formula, E_i is the calculated exposure for the i th RANCH HAND member, q_i is the quantity of TCDD-containing herbicide sprayed from aircraft assigned to the i th subject's base during his assignment, and T_i is the length of the i th subject's assignment (tour length). However, great care must be exercised when applying the above index. For example, the index should be used as an independent regression variable against clinical findings only within occupational strata, to avoid confounding occupational effects with exposure effects. Different degrees of regression between clinical findings and the exposure index can be expected in differing occupational groups since: (a) modes of exposure are likely to be different in different occupational categories, (b) socioeconomic correlates within occupational category could confound an herbicide effect, and (c) other exposures which could synergistically or antagonistically interact with TCDD-containing herbicide may be correlated with occupational category.

Another factor which must be considered when applying this crude exposure index is the problem of confounding a possible herbicide effect with an effect associated with tour length. Being in a combat zone is a major psychophysiological stress, and time spent in such an area may be significantly associated with changes in long term morbidity and/or mortality. This crude exposure index, when used alone, could result in a positive regression with disease incidence or prevalence which is not due to the herbicide exposure. An approach that will correct for this potential confounding is to regress observed medical findings on both E_i and T_i to differentiate the independent effects of herbicide exposure and combat zone experience.

The values of q_i and T_i needed to calculate E_i are generally available from government records. Specifically, tour dates are available from military personnel records, and the quantity of herbicide sprayed is available for the period January 1965 through April 1970 from the "HERBS TAPES." These tapes are comprised of computerized data obtained from actual spray mission reports. This material provides the date, base of mission origin, amount and type of material sprayed (Herbicides Orange, Blue, or White) and location of the intended spray target. Estimates of the amount of herbicide sprayed prior to 1965 may be available from procurement records for Herbicides Purple, Pink, and Green, which were sprayed exclusively from Tan Son Nhut Air Base from 1962 through 1964.

Animal data imply that TCDD is the most toxic component in the herbicides used in RVN. By using q_i , the amount of herbicide sprayed, one is using a variable that roughly correlates with TCDD exposure. However, it would be highly desirable to be able to analyze observed health effects in terms of specific TCDD exposure. The material sprayed from 1965-1970 had significantly lower

TCDD contamination then did those herbicides manufactured and purchased prior to 1962 and used from 1962 through 1964, but due to data limitations from a scarcity of Herbicide Purple, Pink, and Green samples, TCDD concentration profiles for those chemicals cannot be quantitatively determined. However, it may be feasible to develop estimates of the degree of contamination based upon the TCDD concentration from military and manufacturers' data.

As another approach to examining the effect of TCDD itself, one might consider stratifying the exposed cohort by date of assignment in Vietnam, expecting that those assigned earlier were more heavily exposed to TCDD. While it may well be true that earlier assignees were exposed to higher TCDD concentrations, it is unlikely that differences between "early" and "late" assignees, if they occur, can be reliably attributed to TCDD concentration changes, since several potentially confounding variables exist: (a) volunteerism among early assignees, (b) differing assignment patterns between early and late RANCH HANDers (TDY vs long term pattern) and (c) different RVN living conditions.

It is preferable to use an exposure index which is more closely tailored to the specific individual than the crude index discussed above. While T_i is subject specific, q_i is a value which refers to all individuals on the base during the period of time represented by T_i . A refined index for ground crew can be expressed as:

$$E_i = F_i \times q_i \times C \times T_i$$

where,

- F_i = Average flights per day served by the i^{th} ground crew member.
- q_i = Average quantity of herbicide dispensed by flights served by the i^{th} ground crew member.
- C = Estimated TCDD concentration of the herbicides in use during the i^{th} subject's tour of duty.
- T_i = Time spent in TVN in days for the i^{th} ground crew member.

The variable F_i can be estimated by dividing the number of RANCH HAND flights per day by the number of crew chiefs during the time period T_i . All other variables are estimated as with the crude index.

A refined index is also possible for aircrew members and is expressed as follows:

$$E_i = M_i \times D_i \times q_i \times C \times P_i$$

where,

- M_i = total number of missions flown by the i^{th} air crew member.
- D_i = average duration of missions flown by the i^{th} air crew member.
- q_i = average quantity of herbicide dispensed per flight served by the i^{th} air crew member.
- C = estimated TCDD concentration of the herbicides in use.
- P_i = a crew position weighting factor.

As with the refined ground crew index, this refined aircrew index cannot be directly calculated in a strictly quantitative sense using available government records, since records to specifically link missions with particular individuals are not available to objectively determine M_i and D_i . However, reasonably accurate estimates of these parameters may be feasible using questionnaire data. Also air medal awards may allow an indirect estimate of M_i .

The crew position parameter P_i must also rely upon estimations. While the specific crew duties of each subject are known, the differential exposures associated with the crew positions within the C-123 aircraft were not determined during RVN spray missions. The 355th TAS/Spray Branch, Rickenbach AFB OH is presently using the C-123 aircraft, configured with the A/A 45 Y-1 Internal Dispenser and attempts to assess P_i can be made. Air flow measurement and herbicide simulant deposition studies conducted by Meek are performed during the course of four C-123 flights. However, difficulties with the measurement equipment limit the validity of the value of the data in an exposure index. Further work along these lines could yield a more quantitative position weighting factor, P_i , for each individual.

Refined ground crew and air crew exposure indices can be used singly or in combination with the crude exposure index first presented; however, as with the crude index, confounding must be avoided when the refined indices are used in statistical analyses.

The exposure indices listed above are, of course, only applicable to the Ranch Hand cohort. As mentioned, a positive regression of disease incidence or prevalence with increasing exposure index will strongly support herbicide causation. We do not wish to minimize however the role of RANCH HAND versus control group disease incidence/prevalence differences as indicators of a herbicide effect. A major component differentiating the RANCH HANDers from the controls is the increased residence of RANCH HANDers in the RVN itself. If within country time does not correlate with disease incidence, RANCH HAND versus control disease incidence differences may be strongly related to herbicide. If in-country time is significant as a disease correlate, this in itself will be valuable information with regard to assessment of the RVN experience.

VI. Special Statistical Considerations

The previous discussion has outlined the general statistical approach followed by this protocol, and has outlined planned analytical methods and inferential strategies for the mortality, questionnaire and physical examination study phases. This section provides an indepth consideration of some special statistical study aspects.

A. False Reporting/Misrepresentation

Since concern for compensation could unconsciously or consciously influence symptom reporting, and since press reporting itself can stimulate anxiety-based symptom formation, a discussion of false reporting is indicated. A data pattern indicating overreporting has already been discussed in Section V. The goal here is to understand the effect of misrepresentation on estimates of relative risk and the odds ratio. Let S stand for presence of a symptom, and $\bar{S}$ denote its absence. This false reporting may be represented as in Figure 9.

Figure 9

FALSE REPORTING/MISREPRESENTATION

		TRUE STATUS		Total
		S	$\bar{S}$	
REPORTED STATUS	S	A	B	A+B
	$\bar{S}$	C	D	C+D
		A+C	B+D	

The proportion of correctly classified positives is defined by $A/(A+C)$ and is called the sensitivity of the classification scheme; the proportion of correctly classified negatives $D/(B+D)$ is called the specificity.

When there is non-differential misrepresentation, that is, when the sensitivity and the specificity are the same among the exposed and nonexposed, the bias induced in the estimate of relative risk will be toward the null value. The situation is summarized by Figure 10.

Figure 10

MISREPRESENTATION IN RANCH HAND II

		TRUE STATUS					
		Exposed			Nonexposed		
		S	$\bar{S}$	TOTAL	S	$\bar{S}$	TOTAL
REPORTED STATUS	S	a	b	a + b	e	f	e + f
	$\bar{S}$	c	d	c + d	g	h	g + h
		a + c	b + d	n	e + g	f + h	n

Using this representation, the true relative risk is $(a+c)/n + (e+g)/n$, and the apparent relative risk is $(a+b)/n + (e+f)/n$. Figure 11 provides a graphic representation of how apparent relative risk varies as a function of specificity. For this curve, the true relative risk is 2 with the exposed population having a symptom incidence of 0.1 and the nonexposed population having a symptom incidence of 0.05 (Copeland et. al. 1977). The effect of nondifferential false reporting on the odds ratio is nearly as severe as that shown in Figure 11 for relative risk. A technique does exist for correcting the estimate of relative risk to account for false reporting, but the technique requires knowledge of the sensitivity and specificity of the classification scheme; knowledge that may not exist in this study. It should be noted that since the above remarks are concerned with relative risk, the number n of subjects in each group is irrelevant, as the results shown are independent of n.

If the false reporting is differential, an estimate of relative risk that is biased away from the null value can result. This will occur in situations in which the RANCH HAND personnel and controls do not misrepresent their symptoms in the same manner (Copeland et. al. 1977). Thus the "true" outcomes of herbicide exposure may be distorted depending upon the degree and direction of misrepresentation.

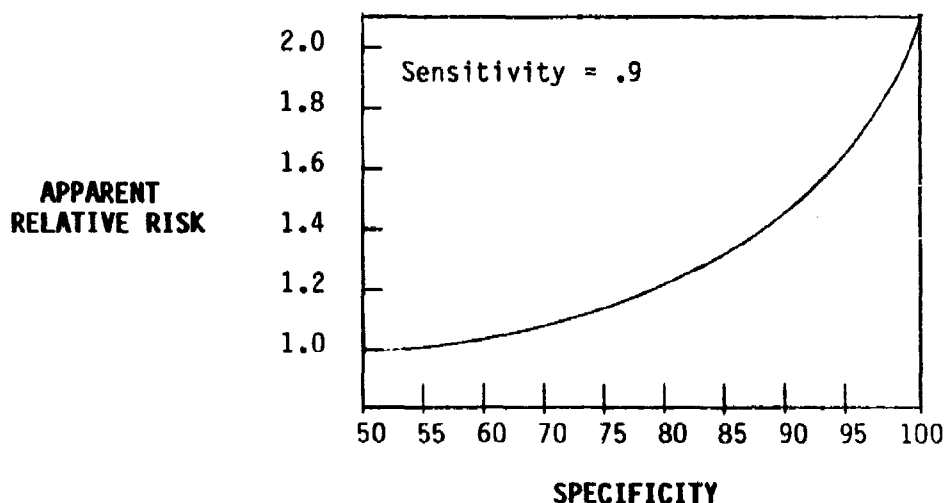
B. Adequacy of Sample Sizes

(1) Overview

The size of the RANCH HAND cohort is approximately 1000 individuals. It is clear that a lethal effect of herbicide which occurs in only 1 out of 2000 controls will be quite difficult to detect unless the herbicide effect is very strong. For example, at a rate of 1 in 2000, 0.5 affected controls are expected. If the basic rate is doubled by herbicide to 2 per 2000, one affected RANCH HAND individual would be expected. At a rate of 1 per 2000 for

Figure 11

APPARENT RELATIVE RISK VERSUS
SPECIFICITY



controls and a rate of 2 per 2000 for RANCH HAND personnel, the probability of observing no affected individuals in both groups is

$$(1 - 1/2000)^{1000} (1 - 2/2000)^{1000} = .22$$

or, in other words, "there is a 22% chance" that no affected individuals will be found in this study. In a population of 100,000 exposed individuals, 100 cases would be expected, 50 of which would be due to herbicide. In short, since the size of the RANCH HAND group is fixed, this study has limited statistical power to define the relationship of herbicide to the rarer diseases.

The power ($1-\beta$) of a study design is the probability that a specified difference between populations will be detected if it in fact exists. In general, power is a direct function of sample size; that is, for a particular study design, the more subjects measured the larger the study power. It is understood that this protocol makes use of the entire known RANCH HAND population (and excludes ancillary exposed groups for reasons previously cited); the exposed sample size cannot be increased. Power augmentation, therefore, can only be accomplished by the less efficient procedure of increasing the control group size which has statistical limitations as well as staggering financial and logistic considerations. Hence, considerable effort has been made to correct loss to study issues (by replacement and other techniques to induce participation) and to use the most powerful statistical design concepts.

Essentially all previous animal and human studies concerning herbicide suffer from a lack of adequate consideration of study power. The following presents a preliminary analysis of study power for the case of continuous and dichotomous variables expected from the study. Also reviewed are alternative studies involving Marine samples.

(2) Power in Continuous Variable Case

Assume that blood cholesterol levels are being compared between RANCH HAND and control groups, and that the coefficient of variation for cholesterol in the control group is 0.1, where the coefficient of variation is the ratio σ_C/μ_C . Assume $\sigma_{RH} = \sigma_C$. The symbol α is the probability that the study will indicate an effect where none exists, and $1-\beta$ is the power as defined before. Consider that the RANCH HAND mean cholesterol μ_{RH} is shifted from the control mean μ_C . A natural question is to inquire about the study power as a function of available pairs (n) and mean ratio $\gamma = \mu_{RH}/\mu_C$.

Table 11

POWER CALCULATIONS

ASSUMPTIONS: $\alpha=0.05$, $\sigma_C/\mu_C=0.1$, $\gamma=\mu_{RH}/\mu_C$

<u>r</u>	<u>γ</u>	<u>Power = 1-β</u>	
		<u>n=180</u>	<u>n=450</u>
.20	1.01	.20	.38
.20	1.02	.55	.88
.20	1.05	>.995	>.995
.70	1.01	.86	.995
.70	1.02	>.995	>.995
.70	1.05	>.995	>.995

Power calculations are displayed in Table 11. Study power in the case of a matched pair design is strongly dependent on the degree of positive correlation produced between the involved groups by the matching procedure. Of course, the degree of correlation can be expressed by the correlation coefficient r which can take values between -1 (negative correlation) and +1 (positive correlation), and two values of r have been employed in Table 11. From this table it is seen that if only 450 pairs are studied a 1% shift in mean (= 1.01) will not be reliably detected, but a 2% shift will be detected with a probability of 0.88 if $r = 0.2$ at least. From this calculation one can infer the need to examine at least 450 pairs to obtain the 2% shift, and to strive for more if possible.

(3) Power in the Dichotomous Variable Case

There is significant discussion in the mathematical statistics literature concerning the efficacy of paired designs in the setting of dichotomous responses (Billewicz, 1974; Ury, 1975; Miettinen, 1970; and several others). Table 12 shows a set of calculations which are applicable to the present study.

Table 12

POWER CALCULATIONS FOR THE DICHOTOMOUS VARIABLE CASE AS A
FUNCTION OF EFFICACY OF PAIRED DESIGNS

P ₁	P ₂	Rel. Risk	r	POWER = 1 - β			
				n=250	n=350	n=450	
.05	.01	5	0	.77	.82	.92	↑ * ↓
.04	.01	4	0	.61	.75	.85	
.03	.01	3	0	.40	.51	.59	
.10	.05	2	0	.61	.75	.85	
.20	.10	2	0	.87	.94	.97	
.05	.01	5	.1	.89/.020	.94/.032	.98/.064	↑ ** ↓
.04	.01	4	.1	.72/.033	.87/.038	.88/.041	
.03	.01	3	.1	.38/.020	.68/.046	.71/.077	
.10	.05	2	.1	.76/.055	.85/.048	.88/.048	
.20	.10	2	.1	.94/.043	.98/.046	.99/.057	

* α = .050

** α = as indicated

In this table, r is again the correlation coefficient indicating the degree of correlation induced between the involved groups by the matching procedure. The probability of the disease among RANCH HAND personnel is symbolized as p₁, while p₂ is the probability of the disease among the controls. Relative risk is the ratio p₁/p₂. With r = 0.1, sign test power tables were used as an exact version of McNemar's test, and therefore different α levels are shown under each power number. Table 12 shows the positive influence of effective

pairing in the higher power levels noted. Also, it appears that for $p_2 = 0.01$ and $p_1 = 0.03$, physical examination of 450 pairs (900 examinations) will disclose the three-fold relative risk with probability less than the minimum target .80. In other words, there is a greater than "20% chance" that a three-fold relative risk on a 1/100 disease state will go undetected in this study if only 350 pairs are examined and if low correlations occur. Once again the need to examine the maximum numbers of pairs in the study is seen.

To present these dichotomous power calculations more clearly, calculations in the context of actual disease states have been accomplished. The diseases considered are cardiovascular disease and cancer, corresponding to high and low rate illnesses for the age groups presently under investigation.

(a) Cardiovascular Disease

A logistic risk function was fitted to data from 17,455 autopsies gathered in a WHO collaborative study in Czechoslovakia, Sweden and the USSR. The function fitted has the form

$$P = [1 + \exp(\alpha + \beta(x-.5) + \gamma(y-.5))]^{-1}$$

where

p = the probability of a complicated coronary lesion

x = age scaled linearly so that $x = 0$ is equivalent to 30 years, and $x = 1$ is equivalent to 58 years (the age span of the current study)

y = 1 or 0 if the subject is exposed or not

and α and β were obtained from the data. The function represents a fairly high rate disease in that at 40 years of age 7% of the group had the lesion, and at 60 years of age 20% had the lesion. The coefficient γ , represents the exposure effect. Power calculations for $\gamma = \beta$ and $\gamma = .8\beta$ are shown in Table 13. This table suggests that if, as a cell toxin, herbicide exposure accelerates cardiovascular disease, this study has a good chance of detecting that acceleration if the herbicide effect is comparable to the age effect. A slight beneficial effect of pairing is seen in this hypothetical example.

(b) Cancer

A logistic risk function was fitted to breast cancer data presented by Breslow and Day (1975). The function fitted represents a low rate disease in that at 35 years of age only .000336 of the group had the lesion while at 70 years of age .00676 of the group will have the lesion.

Using pairing to achieve a power of 0.80 in this setting, 1312 pairs would be needed, when the exposure effect is equal to the age effect. This exceeds the size of our RANCH HAND cohort, and reinforces the fact that herbicide exposure effects on rarer diseases will not have a high likelihood of being detected by this study, and again supports an attempt to examine as many pairs as possible.

Table 13

POWER CALCULATIONS AS A FUNCTION OF HERBICIDE EFFECT

ASSUMPTION. $\alpha = 0.05$

Number of Pairs	$\gamma = \beta$		$\gamma = .8\beta$	
	Power Neglecting Pairing	Power With Pairing	Power Neglecting Pairing	Power With Pairing
100	.93	.93	.54	.53 ($\alpha = .036$)
160	>.97	.98	.81	.82
200	>.99	>.995	.86	.87
250	>.99	>.995	.93	.95
300	>.99	>.995	.96	.97
350	>.99	>.995	.97	.98

(3) Alternative Studies Using Marine Cohorts

The GAO and the National Academy of Sciences have referred to specific Marine cohorts as candidates for a Herbicide Orange epidemiological study. In one suggested study configuration, 5900 marines who were within one half kilometer of a herbicide spray track on the day of spraying are called the exposed group, while 212,100 marines are considered unexposed. In a second suggested study configuration, 21,900 marines within one half kilometer of a spray path within 4 weeks of spraying are considered exposed, while a remaining 196,100 marines are considered unexposed. A mortality study was proposed in both of these study configurations. The mortality phase of this protocol involves approximately 1200 exposed and 6000 control individuals, so that, on the surface, the Marine studies would appear to be more powerful in a statistical sense due to larger numbers. However, in fact, two factors couple to render the marine studies less powerful than the RANCH HAND study detailed in this protocol. First, calculations show that a soldier standing directly

under a spray track at the exact time of spraying receives approximately 1/1000 the dose received by RANCH HAND individuals repeatedly disseminating the mixture throughout the usual RVN tour. Thus even if the unlikely event of being directly under a spray path were repeated 10 times during a marine's RVN tour, the marine's dose would still be only 1/100 that of the RANCH HANDERS. The second factor impacting the Marine study power is the difficulty imposed by the fact that troop positions are only very inexactly known. The available data provide only the battalion headquarter's position relative to herbicide spray paths. Thus troops considered to be exposed could be very far from spray paths, and in fact, be unexposed. On the other hand, troops deemed unexposed in terms of their battalion headquarter's position could in fact have been near spray paths on the day of spraying. Thus, the Marine studies are limited by the problem of misclassification in addition to the fact that the marines received a lesser herbicide exposure than RANCH HAND personnel.

It is possible to compare the RANCH HAND study described in this protocol with the Marine studies in a quantitative way. Results of such an analysis are set out in Tables 14 thru 17. In Table 14, the Marine study using 5900 exposed soldiers is contrasted with the RANCH HAND study considering a disease with an incidence of 0.001 in the control groups, and 0.004 in the RANCH HAND exposed cohort. With a relative risk of 4 against a control disease incidence of 0.001, RANCH HAND power is 0.87 while the Marine study power is much less for several combinations of Marine exposure and misclassification. The misclassification figures shown refers to the percentage inclusion of unexposed individuals into the exposed Marine group. For the calculations, disease incidence in the marine exposed group was assumed to be linearly related to exposure. Table 15 is strictly analogous to Table 14 except that the disease state studied has an incidence of 0.01 in the control groups and 0.02 in the RANCH HAND exposed cohort. Again the RANCH HAND study is seen to be significantly more powerful than the Marine study. Tables 16 and 17 directly parallel Tables 14 and 15, respectively, except that the Marine exposed group is considered to consist of 21,900 soldiers. Here again RANCH HAND study power is seen to be significantly superior.

Figure 12 shows the RANCH HAND mortality study power as a function of relative risk, and disease incidence in the control group. Figure 13 shows marine study power versus marine exposure for zero to 25% misclassification and a control disease incidence of 0.001 and RANCH HAND relative risk of 4. For this circumstance it is clear that the marine study becomes competitive with the RANCH HAND power only if one assumes that the marines received approximately one half of the RANCH HAND exposure dose. Figure 14 is the same as Figure 13 except that 21,900 marines are considered exposed. Again the Marine study becomes competitive with the RANCH HAND study only if one can assume the exposed marines received 0.2 or more of the RANCH HAND exposure, an assumption which is not supported by the available data.

C. The Replacement Concept

In the mortality analysis, a randomly selected group of control individuals will be compared to the RANCH HAND group, and the data gathered will be analyzed for evidence of herbicide effect. In the questionnaire and

TABLE 14

MORTALITY ANALYSIS

POWER COMPARISON OF THE RANCH HAND STUDY TO THE MARINE POPULATION

CONSIDERING MISCLASSIFICATION AND RELATIVE EXPOSURE

POWER TABLE

RANCH HAND POWER 1-B	% MISCLASSIFICATION	MARINE STUDY POWER			
		EXPOSURE LEVELS RELATIVE TO RANCH HAND			
		1/10	1/20	1/100	1/1000
.87	0	.18	.10	.08	.05
	10	.16	.08	.06	.05
	25	.15	.06	.06	.05

ASSUMPTIONS: RH STUDY POP. 1,200: 6,000 (1:5)
MARINE STUDY POP. 5,900: 212,100
NORMAL INCIDENCE OF DISEASE 0.001
DISEASE INCIDENCE IN RH 0.004
LINEAR DOSE - RESPONSE
MISCLASS. OF MARINE CONTROLS EXCLUDED

TABLE 15

MORTALITY ANALYSIS**POWER COMPARISON OF THE RANCH HAND STUDY TO THE MARINE
POPULATION CONSIDERING MISCLASSIFICATION AND RELATIVE EXPOSURE****POWER TABLE**

RANCH HAND POWER 1-B	% MISCLASSIFICATION	MARINE STUDY POWER EXPOSURE LEVELS RELATIVE TO RANCH HAND		
		1/10	1/20	1/100 1/1000
.92	0	.19	.10	.06 .05
	10	.17	.10	.06 .05
	25	.14	.09	.06 .05

ASSUMPTIONS: RH STUDY POP. 1,200; 6,000 (1:5)

MARINE STUDY POP. 5,900; 212,100

NORMAL INCIDENCE OF DISEASE = 0.01

DISEASE INCIDENCE IN RH = 0.02

LINEAR DOSE - RESPONSE

MISCLASS. OF MARINE CONTROLS EXCLUDED

TABLE 16

MORTALITY ANALYSIS**POWER COMPARISON OF THE RANCH HAND STUDY TO THE MARINE
POPULATION CONSIDERING MISCLASSIFICATION AND RELATIVE EXPOSURE *****POWER TABLE**

RANCH HAND POWER 1-B	% MISCLASSIFICATION	MARINE STUDY POWER			
		EXPOSURE LEVELS RELATIVE TO RANCH HAND			
		1/10	1/20	1/100	1/1000
.87	0	.38	.17	.07	.05
	10	.33	.15	.06	.05
	25	.26	.13	.06	.05

ASSUMPTIONS: RH STUDY POP. 1,200; 6,000 (1:5)
 MARINE STUDY POP. 21,900; 186,100
 NORMAL INCIDENCE OF DISEASE = 0.001
 DISEASE INCIDENCE IN RH = 0.004
 LINEAR DOSE - RESPONSE
 MISCLASS. OF MARINE CONTROLS EXCLUDED

* INCORRECT POPULATION
 NUMERICS BASED ON
 ENVIRONMENTAL FATE
 OF TCDD

TABLE 17

MORTALITY ANALYSIS**POWER COMPARISON OF THE RANCH HAND STUDY TO THE MARINE POPULATION
CONSIDERING MISCLASSIFICATION AND RELATIVE EXPOSURE *****POWER TABLE**

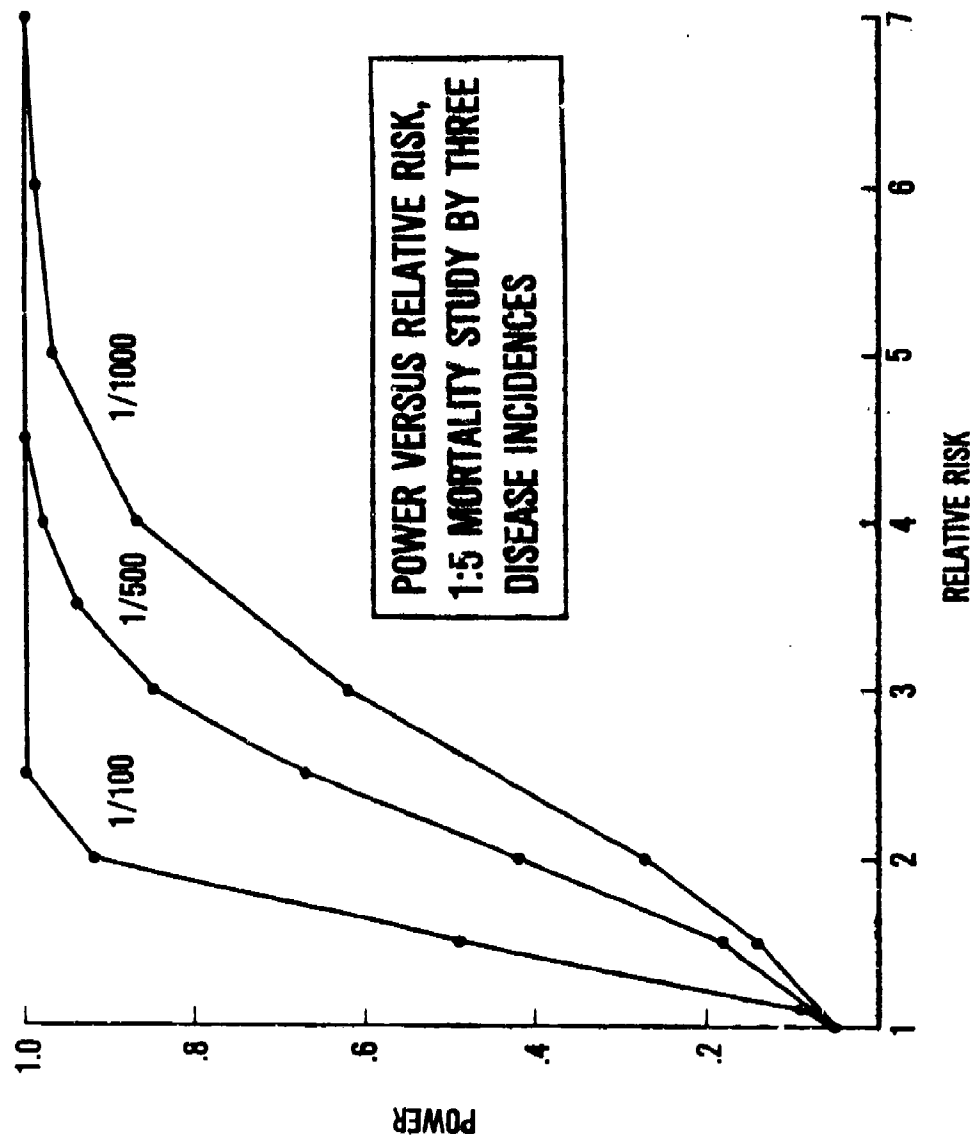
RANCH HAND POWER 1-B	% MISCLASSIFICATION	MARINE STUDY POWER EXPOSURE LEVELS RELATIVE TO RANCH HAND			
		1/10	1/20	1/100	1/1000
.92	0	.41	.17	.07	.05
	10	.36	.16	.07	.05
	25	.28	.13	.06	.04

ASSUMPTIONS: RH STUDY POP. 1,200; 6,000 (1:5)
 MARINE STUDY POP. 21,900; 196,100
 NORMAL INCIDENCE OF DISEASE = 0.01
 DISEASE INCIDENCE IN RH = 0.02

* INCORRECT POPULATION
 NUMERICS BASED ON
 ENVIRONMENTAL FATE
 OF TCDD

LINEAR DOSE - RESPONSE
 MISCLASS. OF MARINE CONTROLS EXCLUDED

FIGURE 12



POWER CURVES OF THE MARINE STUDY CONSIDERING RELATIVE EXPOSURE AND MISCLASSIFICATION OF THE STUDY POPULATION

FIGURE 13

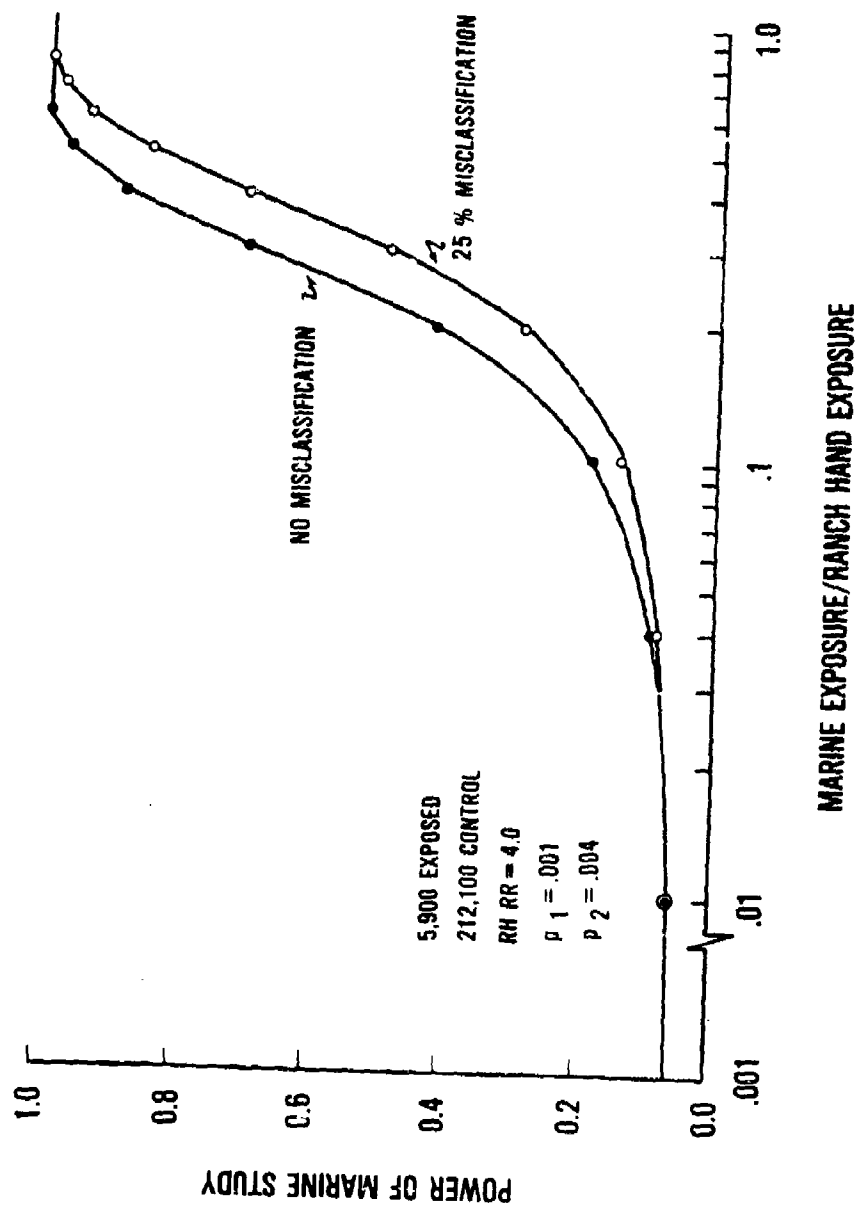
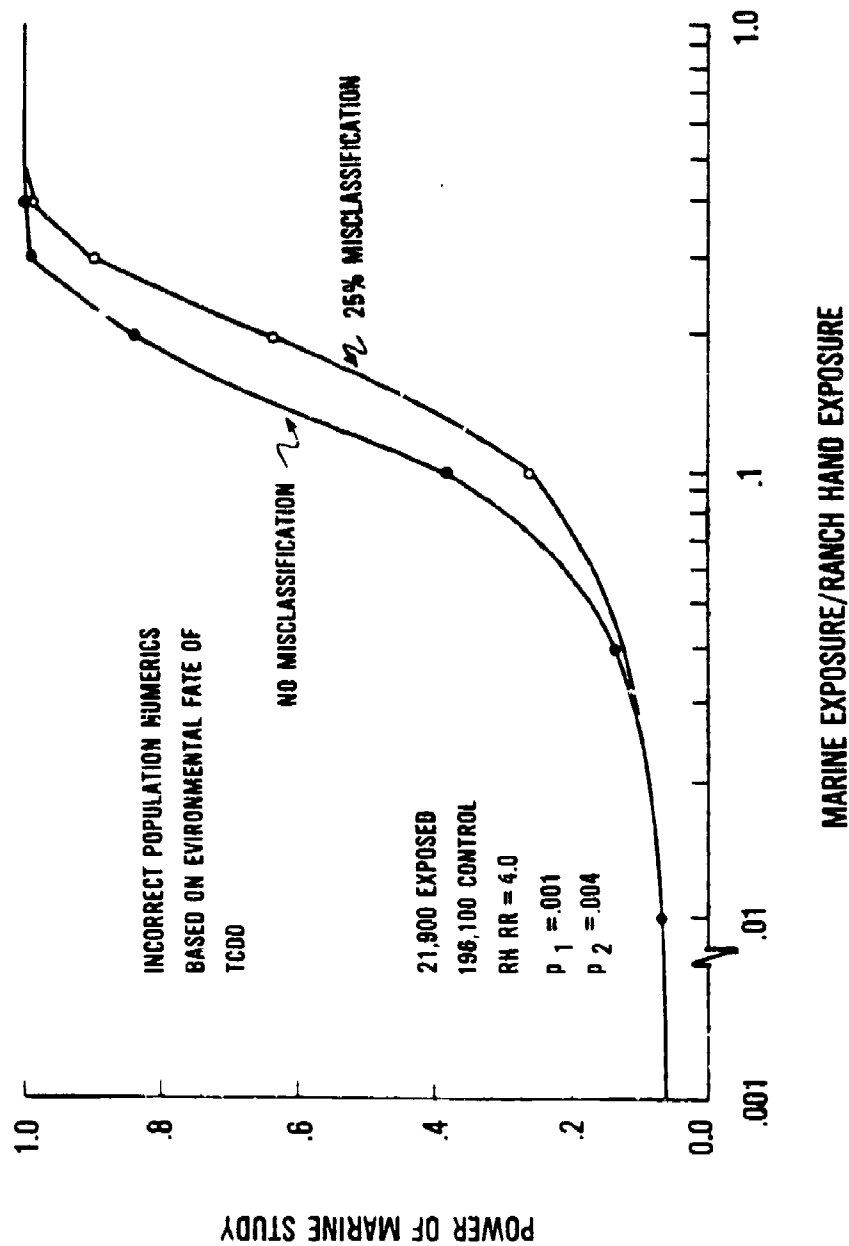


FIGURE 14

POWER CURVES OF THE MARINE STUDY CONSIDERING RELATIVE EXPOSURE AND MISCLASSIFICATION OF THE STUDY POPULATION



physical examination phases of this study, one of the mortality controls will be randomly selected for each RANCH HAND individual. During the physical examination phase, we must anticipate a significant degree of unwillingness to participate, particularly on the part of control personnel. This loss to study can result in significant bias and loss in statistical power; thus the replacement concept has been developed to mitigate these consequences.

In this replacement strategy, we make use of the control individuals matched with each RANCH HAND person. As previously noted, this is accomplished using computerized data files and the matching parameters of age, AFSC, and race. With each RANCH HAND individual R_j there will be associated ten controls $C_{j1}, C_{j2}, C_{j3}, \dots, C_{j10}$. The first of these controls, C_{j1} will be employed in the questionnaire and physical examination phases of the study. If C_{j1} is alive, but unwilling to participate in the study, he will be replaced by another randomly selected participant with similar perception of health status. In order to avoid bias in morbidity analyses, no dead control will be replaced.

It is important to emphasize that all replacement controls will be carefully flagged so that they may be treated separately in the statistical analysis. These replacements will be carefully compared to the lost controls to develop indicators of comparability (e.g., morbidity and mortality experience). The initial analysis will be performed on the intact exposed/control pairs. Additional analysis will be conducted on all pairs, both those intact, and those with replaced controls. If we consider RANCH HAND individual R_j , with living control C_{j1} , we can calculate the probability that control C_{jk} will be available for the 1st, 2nd and 3rd physical examinations. To examine this question, a small computer Monte Carlo simulation was required. A short BASIC language computer program and glossary are included in Appendix Table A-8. This simulation examines the effect of non-participation expressed as two probabilities P_1 and P_2 . Figure A-2 displays the expected participation by the RANCH HAND population, and control group participation is expected to be somewhat less. P_1 is the probability that when first asked to attend a physical examination, the control individual will not comply. P_2 is the probability that a control individual who has agreed once to a physical examination, will not comply for a subsequent examination. In general, P_1 may be greater than P_2 . Note that the probabilities P_1 and P_2 must reflect all causes of non-compliance including morbidity and mortality. Table 18 displays a representative simulation run, which provides the number of controls required to find willing matches for 1000 RANCH HAND personnel.

The potential bias introduced by non-willingness in controls can be analyzed statistically. If $P_C(x)$ is the probability density function for compliant individuals and $P_{NC}(x)$ is the same function for non-compliant individuals, we have

Table 18

CONTROL DISTRIBUTIONS BY EXAMINATION
MATCHING 1000 RANCH HAND PERSONNEL $(P_1 = .70, P_2 = .25)$

CONTROL COHORT	EXAMINATION NUMBER		
	1	2	3
C ₁	318	237	177
C ₂	211	188	156
C ₃	131	133	136
C ₄	96	101	97
C ₅	74	89	90
C ₆	49	68	77
C ₇	34	43	59
C ₈	25	39	52
C ₉	16	18	33
C ₁₀	13	20	35
Number of Matching Failures	33	64	88

$$p(x) = \alpha p_C(x) + \beta p_{NC}(x)$$

where $p(x)$ is the probability density function for the entire population and x is a vector of important health parameters available on each person. Since

$$\int p(x)dx = \int p_C(x)dx = \int p_{NC}(x)dx = 1$$

it follows that

$$\alpha + \beta = 1$$

and α and β may be viewed as coefficients which "mix" the two subpopulations.

If M_C and M_{NC} are the means of the compliant and non-compliant subpopulations respectively, it can be shown that

$$M = \alpha M_n + \beta M_{NC}$$

where M is the mean of the entire population. From this last equation, it is clear that as noncompliant individuals are lost (i.e., β tends to zero, α tends to one), M tends to M_C . Thus the maximum bias is the quantity $M_C - M$.

In this study we propose to replace non-compliant control individuals with matched RANCH HAND control individuals, that is with individuals drawn from a population with density equal to or at least similar to $p_{NC}(x)$. The resulting new density is $p''(x)$ such that

$$p''(x) = \alpha'' p_n(x) + \beta'' \tilde{p}_{NC}(x)$$

where

$$\alpha'' + \beta'' = 1$$

$$M'' = \alpha'' M_n + \beta'' \tilde{M}_{NC}$$

and where $\tilde{p}_{NC}(x)$ approximates $p_{NC}(x)$. If β'' is chosen to be close to or equal to β above, it appears that M'' can well approximate M , the true population mean. The difficulty in this approach will be to assure that the replacements are representative of the non-compliant individuals in all respects other than logistic factors impacting willingness to participate in the program.

Our proposed approach is to obtain sufficient data on the unwilling personnel so that a discrimination function of the form

$$D = f(h_1, \dots, h_i; l_1, \dots, l_i)$$

can be derived. This function is envisioned to have the following properties:

(a) larger values of D correspond to decreasing probabilities of compliance with the physical examination,

(b) the factors h_i relate to the subjects' health status, while the factors l_i relate to logistic difficulties (distance, job) which tend to preclude attendance at the physical. Factors to be considered in the formulation of this function are displayed in Table 19.

(c) D is an increasing function of each h_i and of each l_i ,

Table 19

FACTORS AFFECTING COMPLIANCE

<u>Health Status (h_i)</u>	<u>Logistic Difficulties (l_i)</u>
Subjective Health Assessment (good/poor)	Time Away from Family
Current Utilization of Long-Term Health Care (Yes/No)	Time Away from Job
Absenteeism Pattern (Greater Than/Less Than Ten Lost Days in Past Six Months)	Distance to Examination Site
	Active Pilot
	Income (Greater than/Less than \$17,000)

In the replacement scheme, controls substituted for noncompliant controls, should have identical health factors (h_i) as those individuals they replace. The only significant differences should be in the logistic factors (l_i). The replacement method should permit correction of non-compliance bias given that health factors h_i and logistic factors l_i are actually distinct. The determination of these two classes of factors will be made using data from the study itself. Specifically, the logistic factors l_i will be independent of health status to the degree testable by the quantity of data available in the study. This replacement strategy has two major advantages: selection bias reduction/estimation and cost reduction. Were replacements not employed, one would be compelled to start the morbidity study with a 4 to 1 or 5 to 1 design in order to insure an adequate number of participating controls on the third physical examination (see Table 18). Such a large control group for physical examination is very costly with little

corresponding gain in study power and with no correction of the selection bias.

D. Statistical Analysis of Large Data Sets

A large amount of data will be collected on each subject in this study. Testing at the 0.05 α level means that in 5 out of 100 instances where there has actually been no herbicide effect, a herbicide effect will be falsely inferred. This is the inverse of the power question which concerns the probability of detecting an event when it actually occurs. If 100 independent measures are taken from subjects one should expect, testing at the 0.05 α level, that five measures will be positive on the average. This awareness itself should help prevent over reaction to isolated findings. Further, the present protocol does not in fact have one hundred independent measures. Rather the data gathered are grouped into correlated batteries or systems of data. Findings with any given measure will be related to the values of other correlated variables to provide substantiation indicating an authentic finding.

E. Time-In-Study Effects

The study outlined in this protocol is expected to involve up to six examinations extending over a period of twenty years. It could be anticipated that participation in the study, by increasing the health awareness of the subjects, would tend to improve the health of the cohorts. The possibility of differential participation in the study by the exposed and control groups could bias against finding a herbicide effect if one exists. The control group could be less willing to participate in the study than will the exposed RANCH HAND personnel. Thus, if on the average, controls spend less time in the study than RANCH HANDERS, and under the supposition that increased time in study will correlate with better health, increased RANCH HAND participation would counterbalance any adverse herbicide health effect.

The corrector for this time-in-study effect is simply to study the relationship between health outcome and participation in the RANCH HAND study by regression or other analogous statistical methods. Participation can be quantitated by such metrics as (a) number of physical examinations attended (b) age at physical examinations attended or (c) pattern of physical examination attendance. Special study design features do not need to be incorporated to properly evaluate time-in-study effects on questionnaire and physical examination portions of the study. However, the effects of differential time-in-study on the mortality analysis must be carefully considered. In order to detect time-in-study effects on mortality, individuals whose mortality are being tracked should have been in the study for the same length of time (both exposed and control individuals), or the distribution of time spent in the study should be similar in both groups. Because of anticipated differential participation between the exposed and control groups, one cannot assume that both cohorts will have equal time in study distributions. Steps must be taken to insure that a proper time-in-study distribution occurs in the control mortality group. Control over this distribution is possible through placement of the mortality cohort in the structure of the control group with

respect to the replacement strategy. The following five designs have been considered:

- I. mortality subjects randomized over all ten control positions, and therefore called into the study randomly.
- II. mortality subjects in the first five control positions, and therefore called into the study first.
- III. mortality subjects in positions #1 and #2, with the three remaining subjects randomized into positions #3 through #10.
- IV. mortality subjects in positions #1, #2, #9, and #10, with the one remaining subject randomized in positions #3 through #8.
- V. mortality subjects in the first four positions and position #10.

For each of these five designs, certain quantities were calculated. For testing a physical examination effect on mortality, one would require adequate numbers of mortality subjects having had all six physical examinations, and adequate numbers having had none. Therefore, assuming 1200 RANCH HAND subjects,

E1 = expected number of mortality subjects having all six physical examinations.

E2 = expected number of mortality subjects never asked to take the physical examination.

E3 = expected number of mortality subjects having taken no physical examinations.

For testing or modeling time-in-study effects, one would want adequate numbers of mortality subjects having only one physical, having exactly two physicals, etc. Hence, we calculate, for $J = 1, 2, 3, 4, 5, 6$:

NJ = expected number of mortality subjects taking exactly J physicals (for example N3 is the number of mortality subjects who will have taken three physicals by the end of the study).

and

MJ = expected number of mortality subjects which will actually have taken examination J.

The values of E1, E2, E3, NJ, and MJ have been calculated for the five study designs outlined above using an adaptation of the Monte Carlo program

shown in Appendix Table A8. Best case and worst case situations were considered. In the worst case, it was assumed that when first asked to participate, 75% of the subjects refused, while when asked after having once participated, 50% of subjects refused further contact. In the best case, the first time refusal rate was assumed to be 50%, and the refusal rate for a subject who had participated in a prior examination was assumed to be only 15%. Table 20 shows the calculated results. In examining this table it is of interest to note that the calculated values are not strikingly dependent on study design configuration. However, for both the worst and best cases, design 2 where the mortality subjects are placed in the first five control positions, appears superior and will be used in this study.

Table 20. TIME-IN-STUDY EFFECTS

DESIGN PARAMETERS	WORST CASE					BEST CASE				
	1	2	3	4	5	1	2	3	4	5
E1	18	29	25	22	27	267	521	454	428	504
E2	765	194	580	865	493	3953	2409	3137	3478	2690
E3	4691	4548	4645	4716	4623	4977	4204	4569	4739	4345
N1	700	751	713	681	714	227	370	284	239	331
N2	340	374	347	328	355	185	307	284	239	331
N3	163	188	168	157	177	146	249	189	161	225
N4	71	84	76	72	79	116	203	157	136	188
N5	33	43	36	31	39	94	171	129	110	160
N6	18	29	25	22	27	267	521	454	428	504
M1	18	29				267	521			
M2	14	14				46	77			
M3	24	17				53	83			
M4	40	25				62	94			
M5	54	28				76	107			
M6	80	34				85	116			

VII. Data Repository

Throughout the period of this investigation, data collection methods will be integrated by use of computer systems. A data repository will be established at the USAFSAM. Master files will be formed for each exposed member and for his matched control/controls. The individual master files will be keyed to one or more identifiers. Confidentiality of data will be maintained by the use of computer generated code numbers. Addresses and telephone numbers of all study subjects will be continually updated to insure proper follow-up.

Individual data items and their sources are as follows:

- | | |
|--|--|
| (1) Questionnaire | a. Initial
b. Indepth interview (during physical examination)
c. Follow-up |
| (2) Psychological Battery | a. Initial
b. Follow-up |
| (3) Physical Examination | a. Initial
b. Follow-up |
| (4) Medical Records | a. Active duty
b. VA
c. Civilian
d. Dependent |
| (5) Historical Data | a. Military personnel files
b. Flight records
c. Military unit |
| (6) Death Certificates and Autopsy Reports | a. Study members
b. Dependents |
| (7) Birth Certificates | a. Dependents |

Mortality data will be obtained from individual medical records, VA records, the screening of personnel records, contact with family or personnel physicians, and other available information sources. Date of death (verified by death certificate and available autopsy reports) will be obtained. Cause of death will be expressed as an ICDA number or numbers. The reliability of the mortality data coding will be evaluated by using a dual coding system based on underlying cause of death criteria in use by the National Center for Health Statistics. This will assure that the results of this study are compatible with data based on US mortality statistics. In addition to standard coding for the underlying cause of death, all diagnoses entered on the death certificates will be coded so that multiple cause of death analyses can be conducted.

The computer software for the data analysis phase will be prepared to assure proper data conversion, quality control and standardization of testmeasurements. Quality control areas will include verification of identification data, range checks, and identification/correction of ambiguous or conflicting data.

VIII. Recognized Study Difficulties and Corrective Measures

A. Medical Precedence

(1) Problem

A departure from the usual methodological approach characterizes this particular epidemiological investigation. Clearly there is no historical "roadmap of methodology" to conduct this study. Most occupational exposure studies use the presentation of an unusual disease to justify the initiation of a comprehensive study. A rare disease or a common disease in an uncommon site, or one with an unusual presentation appearing in space-time clusters, (often in an unusual population or age group) usually generates the requirement for a new study. In the case of Herbicide Orange, the evidence for long-term human effects is tenuous and controversial. Despite the unique problems that this study possesses, such as the lack of clinically defined endpoints, there are many problems that it shares with other occupationally related exposure studies. For example, the question of a latent period in the development of symptoms/signs, the lack of accurate dose-response relationships, and the possibility of a synergistic effect with other toxins/carcinogens are all operating in this study. Since most cohort studies of occupational mortality use the general population as a standard for deriving the expected number of deaths, preemployment selection ("healthy worker" bias) affects the comparative experience. Age-standardized mortality ratios (SMR's) in general are 60-90 percent of the standard in the working population. Similar conflicting results can occur using the matched cohort method proposed in this study design. Statistical verification of the validity of utilizing such a control for a summary mortality index (e.g., SMR) has been infrequently attempted in the past. Inability to verify the validity of the more classical methods of comparing mortality will necessitate the use of multiplicative and/or logistic models to obtain a valid standardized mortality ratio.

(2) Corrective Measures

Study approaches generated by unprecedented occurrences of occupationally related medical complaints require novel approaches, and reorientation beyond standard methods. The success key to this study design is a series of effective, progressive, and helpful peer reviews (all of which have occurred to date and have been incorporated herein). Beyond even the immediacy of the current study, is the growing problem of a myriad of occupationally-related exposures, both in the military and civilian sector, which will require similar epidemiological studies in the future in order to make some judgment as to whether or not an association is of causal significance.

B. Group Accountability Bias

(1) Problem

The numerous media presentations on "Herbicide Orange" issues have focused attention on the RANCH HAND group. Several attempts have been

made to construct lists of former members of this group, and thus, the RANCH HAND population should be somewhat easier to locate and contact than the control population. This difference will be particularly evident with respect to reported mortality experience. The incentives for cooperation and study participation are likely to be greater in the exposed group than in the controls. Also, the close knit reunion association of former RANCH HAND personnel will lead to a more precise reporting of morbidity and mortality in that group. Such group identity tends to decrease the degree of unaccountability in the exposed group while its absence in the controls may lead to under ascertainment of mortality. This could then lead to the attribution of excess mortality in the exposed population.

(2) Corrective Measures

Unaccountability bias will be minimized by keeping the percentages of unaccounted for study subjects below 1% in both exposed and control groups. The morbidity and mortality status of all individuals selected for the study will be strongly pursued utilizing a variety of techniques previously described in this document.

C. "Risk Taking" Behavior Bias

(1) Problem

The early RANCH HAND aircrew population was an exclusively volunteer group; the C-130 control population, while volunteers in the Air Force, were not volunteers for special hazardous missions. RANCH HAND mission conditions were considered to be more dangerous than those encountered in the normal combat environment. This suggests that some differences may exist in the psychological profiles of the two groups. A sensation seeking or risk taking psychological orientation may have altered the accident mortality or morbidity patterns of the exposed group. In addition, an accident rate affected by peripheral neuropathy could be masked by undetected risk taking behavior bias.

(2) Corrective Measures

In an attempt to correct for the unique psychological factors that affect the choice of an aeronautical career, and to adjust for the effects of combat stress, transport aircrew members were matched with crewmembers of similar transport aircraft. However, the volunteer nature of the pre-1965 RANCH HAND operation suggests that this basic matching (as an attempt to control for the psychological effects of combat stress) is not totally ideal. The factors of volunteerism and risk-taking behavior must be considered from both the individual and group perspectives. The assessment of individual risk-taking behavior has been quantified by psychological instruments such as the Sensation Seeking Scale (SSS) of Zuckerman, et al. and the Life Experience Inventory (Torrance). The SSS has been demonstrated to have considerable validity in measuring a variety of phenomena including volunteerism and participation in risky activities and has been applied to naval

aviation trainees (Waters). This study was unable to demonstrate an increased accident-related mortality in this group of individuals.

D. Response Bias

(1) Problem

False positive response is anticipated as the primary bias operating in this study. Compensation issues arising from individual claims to the VA or from class action suits, heightened health concern generated by extensive publicity, disenchantment with military service, and the simple desire to please the interviewer may introduce positive responses that exceed the study's ability to correct or adjust. False negative response will also operate, and such bias is even more difficult to assess than the spurious response in a positive direction. Significant factors in this direction include: issues of patriotism and loyalty, personal conviction as to the propriety of the defoliation program and their participation in it, the strong virility orientation of the pilot/aircrew population (particularly with reference to questions of libido and fertility), personal inconvenience caused by study participation, errors of memory, and fear of the adverse effects on career goals that abnormal physical examination results could produce (a significant problem for active civilian and military pilots).

(2) Pending Retirement Bias

The military retirement system also creates a potential source of bias when personnel who are approaching the end of their careers exaggerate their symptoms so that they may become eligible for disability benefits.

(3) Corrective Measures

The primary correction technique for questionnaire response bias will be a carefully constructed and standardized physical examination. Multiple verification and bias indicator questions will be designed and included in the initial questionnaire. Memory verification will be conducted by cross-referencing responses to medical and personnel records. Detailed statistical correlations between the questionnaire responses and the physical examination results will be conducted. All interviews and physical examinations will be conducted on a "blind" basis to the maximum extent possible. Self-administered and group-administered questionnaires, which would allow for uncontrolled response changes, will not be conducted. The payment of a \$100 per day stipend to all eligible participants will be arranged to increase participation rates. Medical data will not be released to agencies such as the Federal Aviation Administration, and therefore civilian flying activities will not be adversely affected by participation in this study. Models of anticipated biases and their estimated impact on the study will be attempted prior to the final analysis of any phase in order to justify the analytic methods used. Conclusions drawn from this study will be predicted and coupled to a bias estimate.

E. Interviewer Bias

(1) Problem

Voice inflection, speed of interview, intonation and ethnicity are recognized factors which can affect positive or negative interview response. These factors will definitely operate in this study.

(2) Corrective Measures

The questionnaire itself will be developed and refined by a civilian contractor. This contractor will assure that the instrument will elicit sensitive personal and medical information in an accurate and efficient manner, while minimizing discomfort to both the subject and the interviewer. All questionnaires will be administered by well-trained and experienced personnel employed by an opinion research organization under contract to conduct this aspect of the study.

F. Changes to the Protocol

(1) Problem

The question of adverse health effects due to Herbicide Orange exposure in Vietnam has evoked many strong emotions. The actions of consumer groups, environmentalists, and other special interest groups have generated defensive responses on the part of some governmental agencies, and reactive decisions by others. Frequently, these responses have been based on unsubstantiated claims and/or scientific evidence of questionable validity. As a result of these governmental actions, the impact on the planning of this study has been substantial. Suggestions to increase the scope of the effort to include other "exposed" individuals or poorly defined ancillary groups continue to surface. However, problems of group ascertainment, exposure validation, control group selection, and control of additional bias make the inclusion of such individuals undesirable from a sound scientific perspective. If such decisions are made without regard for their scientific impact, compromise of study validity is assured.

(2) Corrective Measures

The scientific groups participating in the extensive peer review process agreed with these concerns. The formation of an effective scientific monitoring group will insure that scientific issues will take precedence over emotional pressures to alter the study design when such changes will limit the scientific validity of the study. The dilution of the scientific credibility of this effort by unscientific decisions will be diplomatically resisted. While all suggested improvements will be considered, any alterations or corrections to the study protocol will be based on sound scientific assessments of the proposed changes. Alterations of the protocol will be made only after careful review and analysis by the principal investigators and the monitoring group.

G. Loss to Study/Statistical and Bias Considerations

(1) Problem

Losses to study in the RANCH HAND group pose a major problem to the validity of the inferences that can be made from any subsequent comparisons between or within groups. The avenues of loss will conceivably arise from individual apathy (volunteer bias), lack of appropriate financial reimbursement for loss of salary, the presence or absence of illness (perception of health), and the lack of a desire for "treatment". Losses of matched controls during the questionnaire and physical examination phases of the study, though predictably greater than in the exposed group, may be managed by replacement from the predetermined set of controls. The estimated participation of individuals is shown in Section XV, Figure A-2. It is estimated that the overall response rate of the exposed group will be 65% in the initial questionnaire and 40% in the physical examination phase of the study. These high non-compliance estimates are expected to occur despite great efforts to keep the questionnaire at an acceptable length, and to coordinate questionnaire administration and physical examination with the subject's personal schedule. Losses to study in either the exposed or control groups will obviously lead to decrements in statistical power, and will raise the possibility of severe bias. Losses from the control group are expected to be greater than losses from the exposed set. Such losses would skew the distribution of controls, (Figure 5) and thus alter the characteristics of the population available for study. If differential losses in the control group occur (i.e., "well" controls dropout more frequently than "ill" controls), a "true" herbicide effect would be diluted (Figure 15). Conversely, if "ill" controls are differentially lost, a spurious effect would be attributed to herbicide exposure. To a lesser extent, losses in the exposed group could create similar effects; however, loss to study in the RANCH HAND population should be much less of a problem than in controls, due to their vested interest.

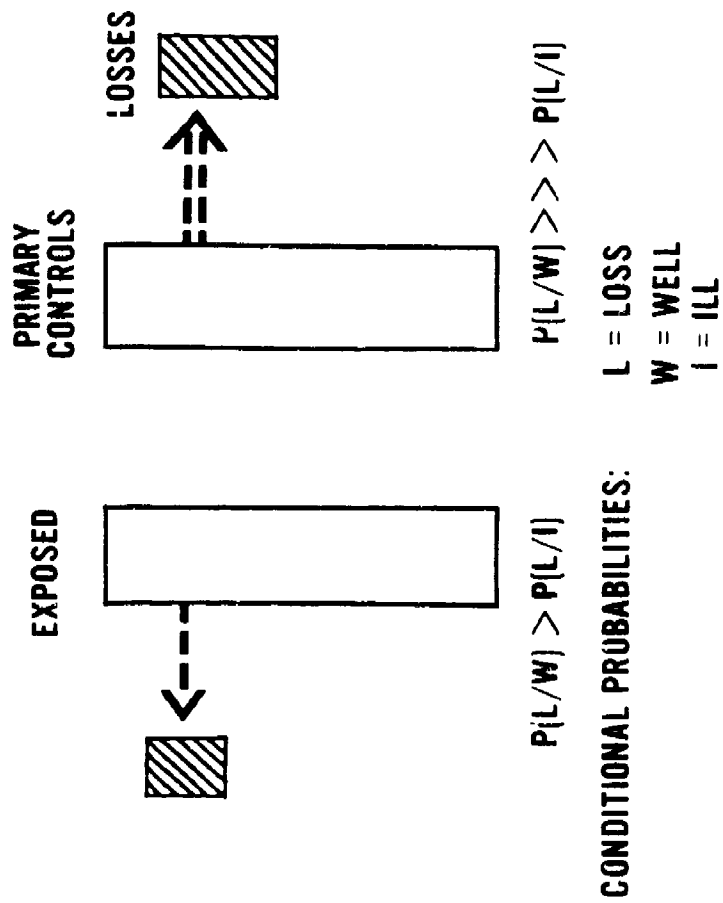
(2) Corrective Measures

The USAF is committed to expending maximal effort to encourage participation. Loss to study problems in the study participants will be avoided as much as possible by detailed and exhaustive efforts to contact and followup each identified participant. **NON-PARTICIPANTS WILL BE STRONGLY ENCOURAGED TO RECONSIDER THEIR INITIAL DECISIONS.** Design considerations have been made to minimize loss to study in both the exposed and control populations. Although the USAF can not fully compensate study subjects for lost wages during the physical examination, transportation costs, per diem, and lodging costs will be reimbursed, and a \$100 per day stipend will be paid to all eligible participants. The replacement concept will help to counteract the decrement in statistical power, and offset the bias created by differential patterns of loss. The exposed group is already of maximum size and cannot be increased, but non-compliant controls can be replaced. This will maximize the degree of pairing between the two study groups. If a non-compliant control is replaced by a control with a similar perception of

FIGURE 15

RATIONALE OF REPLACEMENT

DILUTIONAL BIAS



his own state of health, the alteration of the control group distribution is offset; (i.e., an "ill" control is replaced with an "ill" individual, and a "well" control with another "well" individual.) This concept of replacement, coupled with the payment of stipends, and extensive efforts to encourage compliance will minimize losses to study and offset the adverse effects of those losses that do occur.

H. Statistical Power Limitations

(1) Problem

As discussed in Section VI, statistical power considerations are heavily dependent on loss to study rates. Since the design of the study is also limited by the size of the exposed population, statistical power for identifying the relative risk of an uncommon disease or symptom-complex ($<1/100$) is very low ($<.50$), (See Section VI. B.). This study will, to a greater extent, be able to detect increased risks in common diseases or symptom-complexes ($>1/100$).

(2) Discussion

The "herald sign" of TCDD exposure, chloracne, is expected to have the greatest likelihood of achieving adequate statistical power in this study. Recent findings from Seveso, Italy, support the importance of chloracne as the primary marker symptom. The incidence of chloracne has been reported by Reggiani (personal communication) and Humberger, et al., to be 14.9 cases per 1000 residents in the region of highest contamination of Seveso (Zone A) and 6 to 12 cases per 1000 in the Seveso community as a whole. These rates vary by age group, with children being at highest risk. Only 1 to 5 cases per 1000 were seen in other regions of Northern Italy (Milan, Como, and Lecco). The incidence of adolescent acne in all of these populations varies between 21% and 30%. These incidence rates probably place chloracne at the lower limit of adequate statistical power of this study. In the Nitro, West Virginia studies, residuals of chloracne, as well as exacerbations of previously active disease, continue to be seen 10 years after the most recent exposures, and 30 years after the industrial accident. Thus, it is likely that any chloracne in the exposed population may be detected, despite the intervening years since RANCH HAND exposures. In addition to chloracne, other recently reported human effects of TCDD exposure at Seveso, Italy, appear to fall within the capabilities of this study design (e.g., peripheral neuropathy, neuropsychiatric effects, and liver dysfunction). In general, with respect to statistical power, continuous data (clinical or laboratory measurements, even from relatively small samples) fair much better than either categorical or dichotomous data (presence or absence of a given condition). Consequently, a concerted effort will be made to obtain physical examination data in a scored and/or continuous manner.

I. Variability of Procedures

(1) Problem

The variation of physical examination findings from differences in technique and the random errors inherent in laboratory testing are items of concern, particularly if attributable health effects are subtle or of low magnitude. Nonstandardized procedures and techniques are major contributors to this variance.

(2) Corrective Measures

Variability in examination procedures will be minimized by the use of standardized procedures, examination protocols, on-site monitors, and training. All laboratory procedures will be conducted at the examination center and quality control will be stressed at all times. (See Section IX)

J. Confounding Exposure Factors

(1) Problem

While virtually all of the media attention has been directed toward the 2,4,5-T-containing herbicide formulations, other herbicides were applied concurrently by the C-123 aircrews in Vietnam. Herbicide Blue (Cacodylic acid with 15.4% pentavalent arsenic) and Herbicide White (2,4-D and Picloram) were used throughout the 1962-1970 time period. Any long-term health effects from these additional compounds may confound the results of the study. Peripheral neuritis, tremors, skin and lung cancer, loss of hair and nails, skin rashes, and gastric symptoms have been alleged after exposure to arsenical pesticides. The organophosphate insecticide Malathion was also sprayed by some of these same aircrewmembers when RANCH HAND duties permitted their temporary assignment to mosquito/malaria control missions. Many of these individuals were involved in the aerial spray application of these and other pesticides both before, during, and after their Vietnam service. Long-term effects from these chemicals would confound the study results. The small size of the RANCH HAND population will allow very little opportunity for analytic stratification for these confounding variables. Differing patterns of exposure to aircraft fuels in the study populations have been suggested as confounding factors. The C-130 aircraft were powered by turbo-prop engines which used jet fuel (JP-4), while the C-123 and C-7 aircraft were powered by standard reciprocating engines which used leaded aviation fuel (AV-GAS). After June 1968, many C-123s were modified by the addition of auxiliary jet engine boosters for added power on takeoffs and in emergencies.

(2) Discussion and Corrective Measures

While the extent of confounding caused by exposure to these other pesticides is undetermined at this time, assessment of its magnitude must rely on responses of the subjects to that portion of the questionnaire dealing with other occupational exposures. For this reason, information

concerning exposures to other herbicides/insecticides used in Vietnam will be collected. Whenever possible, stratification techniques will be used to adjust for these confounding variables during data analysis. Variations in fuel between C-130 and C-123 aircraft would be significant factors if individuals in the study were heavily and repetitively exposed. However, the normal duties of the study participants did not involve aircraft refueling or other fuel handling activities. Thus, fuel exposures can be minimized as significant confounding factors.

IX. Quality Assurance and Management Considerations

A. Quality Control

(1) Overview

As in any major scientific effort the quality of the data and the comparability of the data over time are key factors in achieving valid results. Quality assurance in both scientific and management aspects of this study are planned, and will be fully integrated into each phase of the study.

(2) Scientific Aspects

(a) Protocol Development

The Air Force scientific protocol has been under development for more than one year. It has been subjected to an unprecedented five stage independent peer review process to insure the highest quality and validity of its science.

(b) Blind Assessment Protocols

The exposed or non-exposed status of each individual will not be revealed to any of the Health Examiners. Each aspect of the physical examination will be conducted by rigid adherence to the examination protocol. Past medical history and review of systems will be obtained by individuals not associated with the examining process.

(c) Population Ascertainment Quality Control

The study/control populations for this effort were ascertained through extensive computer, and hard copy record searches. The matching variables for each individual were entered and verified with a computer program to minimize transcription errors. Data collection for both exposed and control populations was conducted using identical techniques, thus avoiding systematic bias in population ascertainment.

(d) Precision Matching

Computer techniques will permit extremely close matching of the control participants to the RANCH HAND participants for three distinct variables. This will substantially enhance the analytic flexibility and validity of the study.

(e) Questionnaire Techniques

Detailed questionnaire methods are under development to provide comprehensive crosschecks between objective and subjective health information. Particular emphasis will be placed upon techniques to ascertain false positive information which might impact the validity of the study.

(f) Laboratory Quality Control

The contractor for acquisition of health data mandatorily must have a detailed in-house laboratory quality control program coupled with enrollment into the "CLIA" or "CAP" laboratory survey. In addition, randomly selected duplicate specimens will be sent to a central Air Force reference laboratory for verification.

(g) Single Physical Examination Site

All physical examinations conducted by the contractor will be performed at a single site by dedicated teams of health professionals to insure that data variability is at an absolute minimum. The contractor will be a fully accredited medical institution, and must provide organizational evidence of national/international preeminence.

(h) Personnel Qualifications

All examining physicians will be certified and accredited by a Medical Specialty Board. Paramedics, medical students and interns will not participate as examiners in this study.

(3) Management Aspects

(a) Informed Consent

All participants will be fully informed as to the nature and purpose of all medical diagnostic tests and examinations, and will certify their complete understanding by signing specially designed informed consent forms. Release of medical data will be in strict accordance with Privacy Act determinations, and Air Force policies. Total confidentiality will be granted to subjects who are not on active duty. Active duty subjects will be given limited confidentiality with release of medical information to the DOD only in instances in which there is a risk to public safety or national defense.

(b) Monitoring Group

A monitoring group of scientists and personnel outside the USAF will regularly review and assess the conduct of the RANCH HAND study. This group will interact closely with the Air Force principal investigators, and will provide written commentary and recommendations directly to the White House Office of Science and Technology Policy. Approximately equal representation will be maintained between government scientists, academic scientists, and scientific personnel nominated by veterans advocacy groups.

(c) Consultants

In addition to the structured Air Force management system, outside management and scientific consultants will be utilized to provide assistance to the principal investigators upon request.

(d) Contract Performance

All data acquisition contracts will contain highly detailed schedule performance requirements. All statements of work will be coordinated with two procurement levels, appropriate Air Force program coordinators, and the outside monitoring group.

(e) On-Site Contract Monitor

An Air Force Medical Service officer will be assigned to the physical examination site to:

(1) provide visible Air Force representation to all participants,

(2) conduct detailed entry and exit briefings with all participants, particularly ensuring that the health assessment was conducted on a "blind basis",

(3) review all medical data for completeness and accuracy prior to computer entry, and

(4) examine all relevant features of the data acquisition process, and insure absolute compliance to the contract specifications.

(f) Data Security

All medical information obtained on each participant will be entered into a computer data repository. Access to these data will be limited to key scientific investigators by master code numbers.

B. Management Structure

(1) General Organization

Standard Air Force Systems Command research and development concepts and organization will be used to manage this study and assure effective control of all phases of the investigation. The organizational structure is outlined in Figure 16.

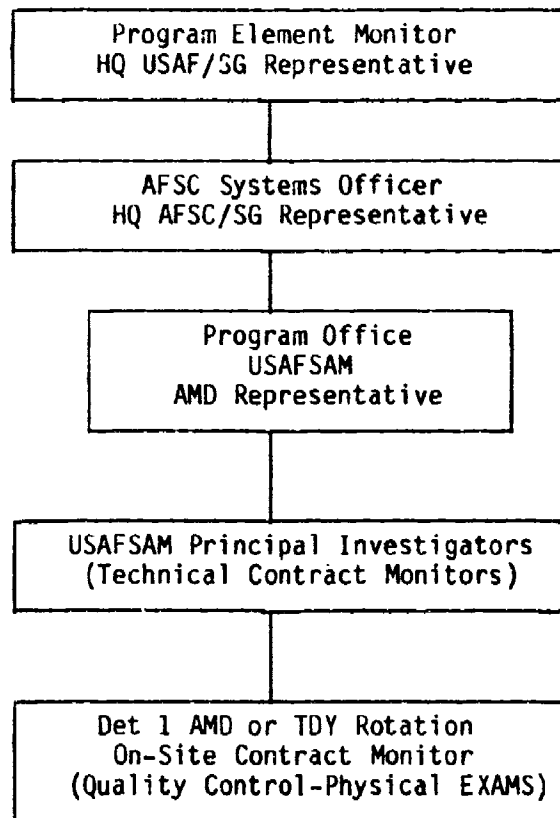
(2) Functions

(a) Program Element Monitor (PEM)

The tasks of the PEM will be performed by a representative of the USAF Surgeon General's staff. The PEM will serve as the Air Staff Program Monitor, and as such, he will represent the needs and interests of the primary investigators to the Surgeon General and the Air Staff. He will support the needs of the study to the Deputy Chiefs of Staff, the Secretary of the Air Force, the Secretary of Defense, and Congress.

Figure 16

MANAGEMENT STRUCTURE



(b) Systems Officer (SYSTO)

The SYSTO will serve as the Program Manager at the Air Force Systems Command level. In this capacity, he will monitor program status, key issues, and problems. He will also serve as coordinator and expediter between the PEM and the primary investigators. Additionally, the SYSTO will prepare program documentation, coordinate all aspects of the program, monitor obligations and expenditures, and initiate reprogramming actions to support unfunded study requirements.

(c) Program Office

The Program Office will be staffed by a representative of the primary investigators and an Aerospace Medical Division (AMD) representative. This office is responsible for implementation of the complete program

management plan on a day-by-day basis. Routine periodic management assessments and program status information will be provided to the SYSTO. The office will assure that all professional and technical aspects meet the stringent quality requirements outlined in the study protocol. It is the responsibility of this office to insure that all schedules, milestones, and financial requirements are met. This office also interfaces with, and provides guidance and support to the onsite contract monitor(s).

(d) USAFSAM Principal Investigators/Scientists

This team is the leading technical resource for this program. Members of this team are responsible for the faithful execution of the protocol, and as such, approve/disapprove all protocol changes, working in concert with the outside monitoring group. The principal investigators are the technical monitors on all contracts under the protocol. They are responsible for the security of all data, for all data analysis, and for all interpretation of analyses subject to review by the outside monitoring group. These investigators provide summary data to Air Force management personnel on request, to enable proper contract billing and program resource analysis. The primary flow of data, data analyses, and analysis interpretation from the principal investigators/scientist directly to the monitoring group is designed to obviate any appearance of Air Force management bias.

(e) Onsite Contract Monitor (Physical Examination Contractor)

The onsite monitor will act as the Air Force representative at the examination site. He will monitor and assess the quality and timeliness of the contractor's performance, and will advise the Program Office of any performance decrements, as well as other problems encountered at the examination site. He will be responsible for the quality control of all aspects of the examination process (physical examination, laboratory procedures, and psychological and physiological testing). He will also welcome each study subject, review the results of the complete evaluation, and debrief each subject at the conclusion of the examination process.

X. Reporting Procedures

Interim synoptic progress reports will be provided to the Surgeon General through Quarterly Management Reviews conducted each January, April, July and October. Key data analyses will be displayed, but inferences and conclusions will await full data analysis at the conclusion of each phase. A formal report for each of the three phases will be completed with forecasted submission dates of: Mortality Study, June 1982; Morbidity Study, June 1983; and Follow-up Study, June 1985, 1987, 1992, 1997, 2002. Findings and conclusions of each phase will be published in a journal of stature. Total study design, findings, and conclusions will be published in the USAFSAM Aeromedical Reviews or Technical Reports.

XI. QUESTIONNAIRE

The release of the actual questions within the questionnaire could possibly result in irreparable damage to the study from an avoidable source of responder bias. Consequently, this section provides a summary of the general subjects to be covered on the questionnaire and a brief discussion of those specific areas that will receive particular emphasis.

The questionnaire will, of necessity, be lengthy, but it will be administered at a time convenient to the subject. Subjects who refuse to participate in a face-to-face interview will be encouraged to cooperate with modified questionnaires given by telephone. The questionnaire will verify personal identification data such as name, SSAN/AFSN, date of birth, address, telephone numbers, race, military status, effective date of status, location of military medical records, and marital history information. RVN tour information will be rechecked and expanded to include specific data such as date of tour, tour end date, AFSC, organization of assignment, PCS and TDY status, combat missions, and whether or not the tour was a RANCH HAND affiliated tour.

Pre- and Post-RVN exposure information, both occupational and avocational, to asbestos, radiation, herbicides, pesticides, and carcinogens will be elicited. Data concerning the frequency and duration of these exposures are very important. RVN exposure to these chemical and physical agents will also be collected.

Medical information obtained during this interview will include a statement of general health, smoking history, alcohol consumption history and long-term medication/drug use. In addition, questions dealing with infertility, birth defects of offspring, as well as the wife's obstetrical history (i.e., total conceptions, live births, miscarriages, stillbirths and premature pregnancies) will be obtained. A family history emphasizing cancer, heart disease, liver disease and inherited disorders in both the subject's and spouse's families will be collected.

A comprehensive medical inventory will be included emphasizing the neurologic, dermatologic, reproductive, and hepatic systems.

At the time of the physical examinations, each subject will be given a comprehensive face-to-face medical history which will expand and verify the health information that was obtained in the initial questionnaire and records review. An extensive review of systems will be covered at that time, including an extensive occupational and avocational exposure history.

Just prior to the time of follow-up adaptive physical examinations, a preliminary telephone contact will establish the subject's current health status and his willingness to continue participation in the study. Appointments for the follow-up examinations will also be arranged. Adaptive questionnaires will be given emphasizing those symptoms and systems that were found to be significantly associated with the exposed population on analysis of earlier study results. If the subject expresses a desire to cease participation at

this time, he will be encouraged to reconsider his decision, and the reasons for dropping out of the study will be sought. At the time of subsequent followup evaluations, subjects who have left the study will be given the opportunity to rejoin the study.

XII. Physical Examination Design

A. General Instructions

This phase of Project RANCH HAND II is a cross sectional study of the subject's health at the time of examination. The physical examination and all required laboratory procedures will be performed by physicians and technicians at a major civilian medical center under contract to the Air Force. It is important that examiners remain unaware of the subject's status as a RANCH HAND participant or as a control subject. The physician examiner is tasked to examine and objectively record his findings. The examining physician is not, and cannot be expected to arrive at any definitive diagnosis, as the full history and laboratory results will not be available to him. Medical history, laboratory results, and physical examination findings will be evaluated by an independent diagnostician employed by the contractor. This diagnostician will formulate diagnoses and differential diagnoses, if appropriate. In addition, he will present a detailed analysis and debriefing to the study subject, and provide a copy of the analysis to the subject's personal physician, if requested.

If, during the examination, the physician discovers evidence of serious illness requiring immediate treatment, the normal emergency or urgent care procedures of the medical facility would apply. Such care will be arranged by the diagnostician and will be supplied by the contractor at Air Force expense. If during the examination, evidence of illness requiring non-emergency medical attention is found, the diagnostician should inform the subject and offer to have forwarded pertinent information to the subject's physician. A clear record of any such advice and treatment should be recorded. The ultimate value of the RANCH HAND II Study will lie in the collection of complete, accurate and, whenever possible, quantitative data permitting the most stringent and powerful statistical analysis. For that reason, the physical examination protocol requires exact measurements in many instances, and the use of defined meanings of semiquantitative indicators in other places.

These examinations will define the health status of the subjects at a point in time, and will establish the presence or absence of abnormal physical findings. After statistical review of the study groups, these findings may permit definition of a chronic effect due to exposure. An inaccurate examination may lead to fallacious study results in two ways: a presumed syndrome may be defined which does not in fact exist, or a syndrome which in fact exists may not be defined with enough validity to warrant further actions.

B. Conduct of the Examination

SECTION		PHYSICAL EXAMINATION		SUBJECT NUMBER
1. GENERAL APPEARANCE				
a. Appearance/Stated Age ☐ Younger Than ☒ Older Than ☐ Same As				
b. ☐ Well-nourished ☐ Obese				
☐ Under-nourished ☐ Older Than				
c. Appearance of illness or distress ☐ Yes ☐ No				
d. Hair Distribution ☐ Normal ☐ Abnormal				
SPECIFY:				
2. HEIGHT cm		WEIGHT (Unshoes) kg		SITTING BLOOD PRESSURE (RIGHT ARM AT HEART LEVEL)
				SYSTOLIC _____ DIASTOLIC _____
3. PULSE RATE REGULAR: ☐ YES ☐ NO Describe any irregularities.				
a. Irregular ☐				
b. Irregularly irregular ☐				
c. VPBs per minute _____				
4. EYE GROUND ☐ NORMAL ☐ ABNORMAL Describe any vascular lesions, hemorrhages, exudates.				
☐ A-V nicking ☐ Hemorrhages ☐ Papilledema				
☐ ↑ light reflex ☐ Exudates ☐ Papilledema				
☐ Arteriolar spasm ☐ Disk Pallor ☐ ↑ Cupping				
5. ARCUS SENILIS ☐ PRESENT ☐ ABSENT 5a. Abnormal Ocular Pigmentation				
☐ Yes ☐ No				
6. ENT ☐ NORMAL ☐ ABNORMAL Describe any abnormality.				
Tympanic membranes intact ☐ Yes ☐ No R ☐ L ☐				
Nasal ulcerations ☐ No ☐ Yes				
7. NECK (Especially thyroid gland) ☐ NORMAL ☐ ABNORMAL Describe any abnormality.				
Thyroid gland palpable ☐ Enlarged ☐ Parotid gland enlargement				
☐ Nodules ☐ R ☐ L				
☐ Tenderness ☐				
8. THORAX AND LUNGS ☐ NORMAL ☐ ABNORMAL Describe any abnormality, especially basilar rales.				
☐ Asymmetrical expansion ☐ Wheezes				
☐ Hyperresonance ☐ Rales				
☐ Dullness				
Circumference at nipple level				
Expiration cm				
Inspiration cm				
9. HEART ☐ NORMAL ☐ ABNORMAL Describe any enlargement, irregularity of rate, murmurs, or thrills.				
Displacement of apical impulse ☐ No ☐ Yes Preordial thrust ☐ No ☐ Yes				
Heart sounds normal ☐ Yes ☐ No ☐ S1 ☐ S2 ☐ S3 ☐ S4				
(Continued in Item 18 on Reverse)				
10. ABDOMEN ☐ NORMAL ☐ ABNORMAL Describe any abnormality with special attention to the epigastrium and liver. Record waist measurement on attached form.				
☐ Hepatomegaly ☐ Other mass - Specify:				
cm Liver Span				
☐ Splenomegaly ☐ Tenderness				
☐ Liver ☐ Spleen ☐ Other, specify:				
11. EXTREMITIES ☐ NORMAL ☐ ABNORMAL Describe any edema or signs of vascular insufficiency.				
☐ Absence, specify:				
☐ Edema				
☐ Pitting ☐ Non-pitting				
☐ Loss of hair on toes				
☐ R ☐ L				
☐ Clubbing of nails				
☐ Varicosities				

SECTION		PHYSICAL EXAMINATION (Continued)			
12. PERIPHERAL PULSES		NORMAL	DIMIN.	ABSENT	COMMENTS
RADIAL					
FEMORAL					
POPLITEAL					
DORSALIS PEDIS					
POSTERIOR TIBIAL					
13. SKIN		☐ NORMAL ☐ ABNORMAL Indicate type and location of lesions on the attached anatomical figure			
☐ Dermatographia ☐ Comedones ☐ Acneiform lesions ☐ Acneiform scars ☐ Depigmentation ☐ Inclusion cysts ☐ Cutis Rhomboidalis		☐ Hyperpigmentation ☐ Jaundice ☐ Spider angioma ☐ Palmar erythema ☐ Full-Face and Bilateral profile photos taken			
		☐ Palmar keratosis ☐ Petechiae ☐ Ecchymoses ☐ Soles of feet ☐ Nails Biopsy Taken			
		☐ Yes ☐ No ☐ Yes ☐ No			
14. MUSCULOSKELETAL		☐ NORMAL ☐ ABNORMAL			
☐ Muscle - Specify: ☐ Weakness ☐ Tenderness ☐ Abnormal Consistency ☐ Atrophy		☐ Spine ☐ Scoliosis ☐ Kyphosis ☐ Tenderness, Level _____ ☐ Decreased range of motion ☐ Pelvic tilt ☐ Straight Leg Raising: Right/Left			
15. GENITOURINARY - RECTAL - HERNIA		☐ NORMAL ☐ ABNORMAL			
☐ Inguinal hernia ☐ R ☐ L ☐ Testes Absent Enlarged Atrophic		☐ Varicocele ☐ Hemorrhoids ☐ Epididymis ☐ Prostatic Enlargement ☐ Scrotal Mass _____ cm dia ☐ Rectal mass			
16. LYMPH NODES - CHECK ALL AREAS.		☐ NORMAL ☐ ABNORMAL - SPECIFY CERVICAL, OCCIPITAL, SUPRACLAVICULAR, AXILLARY, EPITRACHEAL, INGUINAL, FEMORAL			
☐ Enlarged ☐ Tender ☐ Hard ☐ Fixed ☐ Confluent					
17. NERVOUS SYSTEM - SEE ATTACHED FORMS					
18. HEART AND OTHER OBSERVATIONS					
(Continued from Item 9)					
Murmur ☐ No ☐ Yes Area ☐ Ao ☐ Pu ☐ Apex					
Sys ☐ ☐ ☐ ☐					
Dia ☐ ☐ ☐ ☐					
DATE OF EXAMINATION		TYPED OR PRINTED NAME OF EXAMINING PHYSICIAN			
MONTH DAY YEAR					
EXAMINING FACILITY		SIGNATURE			

CLINICAL RECORD

NEUROLOGICAL EXAMINATION

HEAD AND NECK - Normal to Palpations/Inspection ☐ Y ☐ N Specify Scar ☐Asymmetry ☐ Depression ☐Carotid Bruit ☐ No ☐ R ☐ LNeck Range of Motion ☐ Normal or Decreased to ☐ Left ☐ Right☐ Forward ☐ Backward

TRUNK

MOTOR SYSTEM - Handedness Right ☐ Left ☐Gait ☐ Normal or ☐ Broad Based ☐ Ataxic ☐ Small Stepped ☐ Other-SpecifyAssociated Movements ☐ Arm Swing ☐ Normal or Abnormal ☐ R ☐ L

Muscle Status (strength, tone, volume, tenderness, fibrillations)

Bulk ☐ Normal ☐ AbnormalTone Upper Extremities ☐ Normal or ☐ Increased ☐ Decreased☐ Right ☐ LeftLower Extremities ☐ Normal or ☐ Increased ☐ Decreased☐ Right ☐ LeftStrength - Distal wrist extensors ☐ Normal ☐ DecreasedAnkle/Toe Dors/Flexors ☐ Normal ☐ Decreased ☐ R ☐ LProximal Deltoids ☐ Normal ☐ Decreased ☐ R ☐ LHip Flexors ☐ Normal ☐ Decreased ☐ R ☐ LAbnormal Movements (tremors, tics, choreas, etc.) Fasciculations ☐ No ☐ Yes (1-4+)Tenderness ☐ No ☐ Yes (1-4+)Tremor ☐ No ☐ Yes - SpecifyUpper Extremity ☐ R ☐ L ☐ Resting ☐ Essential ☐ IntentionLower Extremity ☐ R ☐ L ☐ Other

Coordination (a) Equilibratory - Eyes Open

Eyes Closed - Romberg ☐ Positive (Abnormal) ☐ Negative (Normal)

Right Foot

Left Foot

(b) Nonequilibratory (F to N; F to F; H to K) Finger-to-nose-to-finger

☐ Normal ☐ Abnormal ☐ Right ☐ Left ☐ BothHeel-Knee-Shin ☐ Normal ☐ Abnormal ☐ Right ☐ Left ☐ Both

(c) Succession Movements (including check, rebound, posture-holding)

If indicated, check ☐ Normal ☐ Abnormal ☐ R ☐ LRapidly alternative movements ☐ Normal ☐ Abnormal ☐ R ☐ L ☐ Both

Skilled Acts

() Handwriting. If indicated, ☐ Normal ☐ Abnormal() Speech (articulation, aphasia, agnosia) Grossly ☐ Normal☐ Abnormal - Specify Dysarthria ☐Aphasia ☐

Reflexes (0-absent; 1-sluggish; 2-active; 3-very active; 4-transient clonus; 5-sustained clonus)

Deep	R	L	Deep	R	L	Other	R	L	Abnormal	R	L
									Babinski		
Biceps			Patellar								
Triceps			Achilles								
Remarks											

MENINGEAL IRRITATION

Straight Leg Raising ☐ Normal ☐ Abnormal ☐ R ☐ L ☐ Both

NERVE STATUS (tenderness, tumors, etc.)

SENSORY SYSTEM (tactile, pain, vibration, position. If positive sensory signs are present, summarize below and indicate details on Anatomical Figure, Std. Form 531)

Light Touch ☐ Normal ☐ Abnormal

Pin Prick ☐ Normal ☐ Abnormal (Map on Anatomical Figure)

Vibration (at ankle, 128 hz tuning fork): ☐ Normal ☐ Abnormal ☐ R ☐ L ☐ Both

Position (Great toe): ☐ Normal ☐ Abnormal ☐ R ☐ L ☐ Both

CRANIAL NERVES

I R Smell ☐ Present ☐ Absent

L Smell ☐ Present ☐ Absent

II Fundus R Normal ☐ Abnormal ☐ Disk Pallor/atrophy
☐ Exudate ☐ Papilledema ☐ Hemorrhage

Fundus L Normal ☐ Abnormal ☐ Disk pallor/atrophy
☐ Exudate ☐ Papilledema ☐ Hemorrhage

Fields (to confrontation)

Right ☐ Normal ☐ Abnormal Left ☐ Normal ☐ Abnormal

III Normal ☐ ☐ Abnormal - Specify

IV Pupils-Size (mm) Equal ☐ Unequal ☐ Difference mm _____

VI Shape, position Round ☐ Other ☐ R ☐ L

Light, Reaction Normal ☐ Abnormal ☐ R ☐ L

Position of Eyeballs

Movements R

L

Nystagmus Rotary ☐ Horizontal ☐ Vertical ☐
 (Draw position)

XI

Ptosis R ☐ L ☐

V Motor R Clench Jaw - Symmetric ☐ Deviated ☐ R ☐ L ☐

Sensory R Normal ☐ Abnormal ☐ V1 ☐ V2 ☐ V3 ☐
 L Normal ☐ Abnormal ☐ V1 ☐ V2 ☐ V3 ☐

Corneal Reflex R ☐ L ☐

VII Motor R Normal smile ☐ Yes ☐ No Palpebral Fissure ☐ Yes ☐ No
 L Normal smile ☐ Yes ☐ No Palpebral Fissure ☐ Yes ☐ No

IX Palate and Uvula
 X Movement Normal ☐ Deviation to ☐ R ☐ L
 Palatal Reflex R ☐ Normal ☐ Abnormal
 L ☐ Normal ☐ Abnormal

XII Tongue-Protruded-Central ☐ R ☐ L ☐
 Atrophy ☐ No ☐ Yes

MENTAL STATUS (alert, clear, cooperative, etc.) Gross abnormalities: ☐ No
☐ Yes - Specify

DIAGNOSTIC SUMMARY
SYNOPSIS OF POSITIVE FINDINGS

Medical History:

Physical Examination:

General

Dermatologic

Neurological

Psychological

Laboratory Results:

Diagnosis:

Differential Diagnosis, if applicable:

Date

Signature
of Diagnostician

C. Special Procedures

(1) Nerve Conduction Velocities (NCV)

These studies have been determined to be an important parameter in long-term follow-up studies of persons thought to have been exposed to Herbicide Orange components. The Nerve Conduction Velocities should be performed by a physician or by a specialty qualified technician under the supervision of a physician trained in neurophysiological methods.

(a) Specific NCVs

(1) Ulnar Nerve (one side only)

(a) motor (above elbow, below elbow)

(b) values recorded

(i) distal latency

(ii) NCV

(2) Peroneal Nerve (one side only)

(a) motor

(b) values recorded

(i) distal latency

(ii) NCV

(3) Sural Nerve (one side only)

(a) sensory: orthodromic

(b) values recorded: NCV

(b) Methods

Standardized, published methods will be used (e.g., Smorto, Marcio P., and John V. Besmajian; Electrodiagnosis; Harper and Row; NY, 1977).

(2) Psychological Test Battery

(a) General

This battery yields objective numerical data, and is well-standardized and clinically validated. The individual tests were chosen to insure an adequate analysis of one of the major alleged manifestations of

Herbicide Orange toxicity. Each test either validates the other tests or is considered to be a "definitive" test for analysis of a suspected psycho-neuro-pathic effect under study. Compared to the general civilian population, characteristic response tendencies are observed on the MMPI and Cornell Index among active duty aircrewmembers being evaluated in an aeromedical setting. It is also important to consider the effect that pending retirement has exerted on the reporting of medical history and symptomatology. This may also alter responses to psychological testing.

(b) Specific Tests

(1) Wechsler Adult Intelligence Scale (WAIS)

Individually-administered collection of verbal and nonverbal intellectual measures; also useful for clinical inferences when combined with the neuropsychological battery below.

(2) Reading subtest of the Wide Range Achievement Test (WRAT)

Individually-administered measure of word recognition ability. Important to rule-out reading inefficiency should the response to the personality instruments below be of questionable validity (e.g., high F scale on MMPI).

(3) Halstead-Reitan Neuropsychological Test Battery

Individually-administered collection of brain behavior relationship measures for establishing the functional integrity of the cerebral hemispheres. The battery must include the following subtests: Category, Tactual performance, Speech-Sounds, Seashore Rhythm, Finger Tapping, Trail Making, and Grip Strengths. The Aphasia Screening and Sensory-Perceptual Exams are considered optional in view of their redundancy with the clinical neurologic exam included in this project. Individualized test debriefing is conducted to clarify test performances in the WAIS and Neuropsychological Battery.

(4) Three subtests of the Wechsler Memory Scale I (WMS I)

Individually-administered measures of immediate and delayed recall of verbal and visual materials. The Logical Memory, Associate Learning and Visual Reproduction subtests are to be administered in the standard, immediate-recall fashion initially. After 30 minutes has elapsed, the examinee is asked, without prior alerting, to recall as much as he can about the Logical Memory and Visual Reproduction subtest stimuli. Standard scoring is used for both test-retest administrations.

(5) Cornell Index (CI)

Self-administered and standardized neuropsychiatric symptom and complaint inventory, including items involving asthenia, depression, anxiety, fatigue, and GI symptoms in lay language. Endorsement of items are to be explored and clarified in test-debriefing.

(6) Minnesota Multiphasic Personality Inventory (MMPI)

60 to 90 minute self administered clinical psychiatric screening instrument; also capable of estimating response biases (e.g., "fake good," or "fake bad"). The shortened version of Form R (i.e., items 1 to 399) may be substituted for the 566-item Long Form. Standard scoring and Minnesota norms are to be used, with the possible exception of active duty examinees where USAFSAM aircrew norms may be applied. Clarification of profiles showing response biases, questionable validity, and/or unusual item endorsements will be conducted in individual test debriefing.

(3) 12-Lead Electrocardiogram

(a) Procedures

A standard 12-lead scalar electrogram is required. If an arrhythmia is observed, a one minute rhythm strip will be obtained. The electrogram will be done following a minimum fast of four hours.

(b) Interpretation

The electrocardiograms will be interpreted by cardiologists at the examining center, and then forwarded to Brooks AFB where physicians in the USAF Central ECG Library will compare the tracing to previous individual ECG records in the case of rated (pilot or navigator) subjects.

(c) Disposition (USAF Central ECG Library)

(1) Pilots and Navigators

The original tracings will be microfished and permanent record established for each individual.

(2) Enlisted Subjects

The original tracings will be microfished and a permanent record established for each individual.

(4) Radiographic Examination

A standard 14x17 in., standing, roentgenogram in the PA position using small nipple markers will be accomplished.

(5) Pulmonary Function Studies

Standard evaluation of vital capacity and forced expiratory volume at 1 second will be performed.

(6) Laboratory Procedures

(a) Specific Tests to be Performed on all Participants

- (1) Hematocrit
- (2) Hemoglobin
- (3) RBC Indices
- (4) White Blood Cell Count and Differential
- (5) Platelet Count
- (6) Erythrocyte Sedimentation Rate
- (7) Urinalysis
- (8) Semen Analysis (Number, % Abnormal, Volume)
- (9) Blood Urea Nitrogen
- (10) Fasting Plasma Glucose
- (11) Creatinine
- (12) 2-hour Post Prandial Plasma Glucose
- (13) Differential Cortisol (0730 and 0930 hours)
- (14) Cholesterol & HDL
- (15) Triglycerides
- (16) SGOT
- (17) SGPT
- (18) GGTP
- (19) Bilirubin, Total and Direct
- (20) Alkaline Phosphatase
- (21) LDH

- (22) Serum Protein Electrophoresis
- (23) CPK
- (24) VDRL
- (25) LH
- (26) FSH
- (27) Testosterone
- (28) Thyroid Profile (RIA) (T₃, T₄, TSH,FTI)
- (29) Delta-aminolevulinic Acid
- (30) Urine Porphyrins
- (31) Hepatitis B antigen/antibodies
- (32) Prothrombin time
- (33) Blood Alcohol

(b) To be performed on selected subjects

(1) Anti-nuclear Antibody on subjects with indications of autoimmune disorders

(2) Hepatitis A Antigens/antibodies for those with current or past history of liver disease

(3) Karyotyping for those fathering children with birth defects

(4) Skin photography and skin biopsy on subjects with suspected chloracne

(5) To be performed if medical history indicates a subject has an increase in infectious diseases:

(a) Immuno-electrophoresis

(b) Quantitative Immunoglobulin Determinations

subjects (6) To be performed on a randomly selected group of

(a) Enumeration of B and T cells

(b) Enumeration of Monocytes

(c) B and T cell function tests

(7) Rationale for laboratory procedures

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

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

(2) Reticuloendothelial System: Thymic atrophy, altered cellular immunity, decreased lymphocyte counts.

(3) Hemopoietic System: Anemia, thrombocytopenia, leukopenia, pancytopenia.

(4) Endocrine System: Hemorrhage and atrophy of adrenal cortex, hypothyroidism.

(5) Renal: Increase in blood urea nitrogen.

(6) In addition, statistically significant increases in hepatocellular carcinomas (liver) and squamocellular carcinomas of the lung were found.

(b) Studies on the toxic effects of TCDD in man have shown that the following organ systems are damaged:

(1) Skin: Chloracne, hirsutism.

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

(3) Renal: Hemorrhagic cystitis, focal Pyelonephritis.

(4) Neuromuscular System: Asthenia, i.e., headache, apathy, fatigue, anorexia, weight loss, sleep disturbances, decreased learning ability, decreased memory, dyspepsia, sweating, muscle pain, joint pain and sexual dysfunction.

(5) Endocrine System: Hypothyroidism.

(c) Based upon the reports of toxic effects in animal and human exposures, the following organ panels were thus recommended:

- (1) Hemopoietic
- (2) Reticuloendothelial
- (3) Renal
- (4) Endocrine
- (5) Neuromuscular

(d) Hemopoietic screening should include:

- (1) Hematocrit
- (2) Hemoglobin
- (3) RBC indices
- (4) Erythrocyte sedimentation rate
- (5) Platelet count
- (6) Prothrombin time

(e) Reticuloendothelial system:

- (1) White blood cell count
- (2) Differential
- (3) Serum protein electrophoresis
- (4) Selective use of immunoelectrophoresis and quantitative immunoglobulin determination
- (5) B cell and T cell counts and functions

(f) Hepatic screen:

- (1) SGOT
- (2) SGPT
- (3) GGTP

- (4) Bilirubin, Total and Direct
- (5) Alkaline phosphatase
- (6) LDH
- (7) Cholesterol
- (8) HDL
- (9) Triglyceride
- (10) Urine prophyryns
- (11) Urine porphobilinogen
- (12) Hepatitis B antigens/antibodies
- (g) Renal screen:
 - (1) Urinalysis
 - (2) BUN
 - (3) Creatinine
- (h) Endocrine screen:
 - (1) Differential cortisol (0730 and 0930 hours)
 - (2) Thyroid profile (RIA)
 - (3) Fasting plasma glucose
- (i) Neuromuscular system:
 - (1) CPK
- (j) Elucidation of sympoms of asthenia:
 - (1) Testosterone
 - (2) LH
 - (3) FSH

(k) The following tests should be performed only as follow-up for abnormalities in the history or physical examination findings:

(1) HAVAB (IgG and IgM)

(2) ANA

XIII. PRINCIPAL INVESTIGATORS, CO-INVESTIGATORS AND CONTRIBUTORS

A. PRINCIPAL INVESTIGATORS

George D. Lathrop, MD, MPH, PhD
Colonel, USAF, MC
Chief, Epidemiology Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

William H. Wolfe, MD, MPH
Lt Colonel, USAF, MC
Chief, Disease Surveillance Branch
Epidemiology Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

Richard A. Albanese, MD, GS-15
Chief, Biomathematical Modeling Branch
Data Sciences Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

Patricia M. Moynahan, BSN, MS,
Lt Colonel, USAF, NC
Chief, Occupational Epidemiology Branch
Epidemiology Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

B. CO-INVESTIGATORS

Alvin L. Young, BS, MS, PhD
Major, USAF
Special Assistant on Military Herbicides
Department of Environmental Medicine
Veterans Administration
810 Vermont Ave NW
Washington DC, 20420

Clarence F. Watson, Jr., MD, MPH
Colonel, USAF, MC
Chief, Clinical Sciences Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

James A. Wright, MD, MPH
Major, USAF, MC
Assistant Chief, Disease Surveillance Branch
Epidemiology Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

Joel E. Michalek, PhD, GS-13
Mathematical Statistician
Data Sciences Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

Phelps P. Crump, PhD, GS-15
Chief, Consultation & Training Branch
Data Sciences Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

Richard C. McNee, MS, GS-14
Chief, Advanced Analysis Branch
Data Sciences Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

Alton J. Rahe, MS, GS-13
Mathematical Statistician
Data Sciences Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

Michael A. Sauri, MD, MPH & TM
Major, US Army, MC
Department of Internal Medicine
Brook Army Medical Center
Fort Sam Houston, TX 78234

Richie S. Dryden, MD, MPH
Lt Colonel, USAF, MC
Chief, Flight Medicine Branch
Clinical Sciences Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

C. CONTRIBUTORS

Thomas V. Murphy, MBA, GS-9
Statistician
Disease Surveillance Branch
Epidemiology Division
USAF School of Aerospace Medicine
Brooks AFB, TX 78235

Robert A. Bottenberg, PhD, GS-15
Chief, Computational Sciences Division
AF Human Resources Laboratory
Brooks AFB, TX 78235

Jimmy D. Souter, BA, GS-14
Chief, Analysis & Programming Branch
Computational Sciences Division
AF Human Resources Laboratory
Brooks AFB, TX 78235

Calvin C. Fresney, GS-12
Chief, Data Base Management Section
Computational Sciences Division
AF Human Resources Laboratory
Brooks AFB, TX 78235

Henry W. Clark, BA, GS-12
Supervisory Computer Systems Analyst
Computational Sciences Division
AF Human Resources Laboratory
Brooks, AFB, TX 78235

Phillip G. Brown, BS, MS
Major, USAF, BSC
Assistant for Bioenvironmental Engineering
Office of the USAF Surgeon General
Bolling AFB, MD 20332

XIV. SELECTED BIBLIOGRAPHY (Key References)

A. GENERAL REFERENCES

Meek, Stephen L., An estimate of the relative exposure of U.S. Air Force crewmembers to agent orange. Masters degree thesis, University of Washington, School of Public Health and Community Medicine, Seattle, 26 February 1981.

Young, A. L., J. A. Calcagni, C. E. Thalken and J. W. Tremblay. 1978. The toxicology, environmental fate, and human risk of Herbicide Orange and its associated dioxin. USAF Occupational and Environmental Health Laboratory, Brooks Air Force Base, Texas. Technical Report OEHL-TR-78-92. 247 p.

International Agency for Research on Cancer. 1978. IARC Internal Technical Report No. 78/001. Coordination of epidemiological studies on the long-term hazards of the chlorinated dibenzo-dioxins/chlorinated dibenzofurans. Joint NIEHS/IARC Working Group Report. Lyon, France. 44 p.

Report by the Comptroller General of the United States. April 7, 1979. Health effects of exposure to Herbicide Orange in South Vietnam should be resolved. General Accounting Office Pub. CED-79-2. 38 p.

B. PHARMACOKINETICS OF 2,4-D

Berndt, W. O. and F. Koschier. 1973. In vitro uptake of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) by renal cortical tissue of rabbits and rats. Toxicol. Appl. Pharmacol. 26:559-570.

Clark, D. E., J. S. Palmer, R. D. Radeleff, H. R. Crookshank and F. M. Farr. 1975. Residues of chlorophenoxy acid herbicides and their phenolic metabolites in tissues of sheep and cattle. J. Agric. Food Chem. 23(3):573-578.

Elo, H. and P. Ylitalo. 1977. Substantial increase in the levels of chlorophenoxyacetic acids in the CNS of rats as a result of severe intoxication. Acta Pharmacol. Toxicol. 41:280-256.

Ume, K. 1966. Distribution and elimination of chlorinated phenoxyacetic acids in animals. Acta Vet. Scand. 7:264-271.

Grunow, W. and C. Bohme. 1974. Über den stoffwechsel von 2,4,5-T und 2,4-D bei ratten und mausen. (Metabolism of 2,4,5-T and 2,4-D in rats and mice.) Arch. Toxicol. 32:217-225. (German)

Khanna, S. and S. C. Fang. 1966. Metabolism of ¹⁴C-labelled 2,4-dichlorophenoxyacetic acid in rats. J. Agric. Food Chem. 14(5):500-503.

International Agency for Research on Cancer. 1977. 2,4-D and esters. P. 111-199. In IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 15. Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins, and Miscellaneous Industrial Chemicals. Lyon, France.

C. PHARMACOKINETICS OF 2,4,5-T

Bohme, C. and W. Grunow. 1974. Uber den stoffwechsel von 4-(2,4,5-trichlorophenoxy)-buttersaure bei ratten. (Metabolism of 4-(2,4,5-trichlorophenoxy)-butyric acid in rats.) Arch. Toxicol. 32:227-231. (German)

Dencker, L. 1976. The herbicide 2,4,5-T: Early placental barrier and accelerated fetal uptake with advancing gestation. P. 59-79. In Tissue Localization of Some Teratogens at Early and Late Gestation Related to Fetal Effects. Acta Pharmacol. Toxicol. 39(Suppl 1): 131p.

Ebron, M. And K. D. Courtney. 1976. Difference in 2,4,5-T distribution in fetal mice and guinea pigs. Toxicol. Appl. Pharmacol. 37:144-145.

Fang, S. C., E. Fallin, M. L. Montgomery and V. H. Freed. 1973. The metabolism and distribution of 2,4,5-trichlorophenoxyacetic acid in female rats. Toxicol. Appl. Pharmacol. 24:555-563.

Lindquist, N. G. and S. Ullberg. 1971. Distribution of the herbicides of 2,4,5-T and 2,4-D in pregnant mice: Accumulation in yolk sac epithelium. Experientia 27:1439-1441.

Piper, W. N., J. Q. Rose, M. L. Leng and P. J. Gehring. 1973. The fate of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) following oral administration to rats and dogs. Toxicol. Appl. Pharmacol. 26:339-351.

Sauerhoff, M. W., W. H. Braun, G. E. Blau and P. J. Gehring. 1976. The dose-dependent pharmacokinetic profile of 2,4,5-trichlorophenoxy acetic acid following intravenous administration to rats. Toxicol. Appl. Pharmacol. 36:491-501.

D. PHARMACOKINETICS OF TCDD

Allen, J. R., J. P. Van Miller and D. H. Norback. 1975. Tissue distribution, excretion and biological effects of [¹⁴C] tetrachlorodibenzo-p-dioxin in rats. Food Cosmet. Toxicol. 13:501-505.

Piper, W. N., J. Q. Rose and P. J. Gehring. 1973. Excretion and tissue distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Advan. Chem. Ser. 120:85-91.

Reggiani, G. 1978. The estimation of TCDD's toxic potential in the light of the Seveso accident. 20th Congress of the European Society of Toxicology, Berlin (West), June 25-28. 20p.

Rose, J. Q., J. C. Ramsey, T. H. Wintzler, R. A. Hummel, and P. J. Gehring. 1976. The Fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin following single and repeated oral doses to the rats. *Toxicol. Appl. Pharmacol.* 36:209-226.

Vinopal, J. H. and J. E. Casida. 1973. Metabolic stability of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian liver microsomal systems and in living mice. *Arch. Environ. Contam. Toxicol.* 1(2):122-133.

E. PHARMACOKINETICS OF 2,4-D and 2,4,5-T IN MAN

Coutselinis, A., R. Kentarchou and D. Boukis. 1977. Concentration levels of 2,4-D and 2,4,5-T in forensic material. *Forensic Sci.* 10:203-204.

Gehring, P. J., C. G. Kramer, B. A. Schwetz, J. Q. Rose and V. K. Rowe. 1973. The fate of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) following oral administration to man. *Toxicol. Appl. Pharmacol.* 26:352-361.

Kohli, J. D., R. N. Khanna, B. N. Gupta, M. M. Dhar, J. S. Tandon and K. P. Sircar. 1974. Absorption and excretion of 2,4-dichlorophenoxyacetic acid in man. *Xenobiotica* 4(2):97-100

Kohli, J. D., R. N. Knanna, B. N. Gupta, M. M. Dhar, J. S. Tandon and K. P. Sircar. 1974. Absorption and excretion of 2,4,5-trichlorophenoxyacetic acid in man. *Arch. Int. Pharmacodyn. Ther.* 210:250-255.

Nielsen, K., B. Kaempe, and J. Jensen-Holm. 1965. Fatal poisoning in man by 2,4-dichlorophenoxyacetic acid (2,4-D).

Ramsey, J. C., T. L. Lavy, and W. H. Braun. 1979. Exposure of forest workers to 2,4,5-T: Calculated dose levels. Toxicology Laboratory, Dow Chemical Company USA, Midland, Michigan. Mim. Unpublished data, 32p.

Sauerhoff, M. W., W. H. Braun, G. E. Blau and P. J. Gehring. 1977. The fate of 2,4-dichlorophenoxyacetic acid (2,4-D) following oral administration to man. *Toxicology* 8:3-11.

F. CELLULAR MECHANISMS OF ACTION OF TCDD

Crow, K. D. 1970. Chloracne. *Trans. St. John Hosp. Derm Soc.* 56:79-99.

Courtney, K. D. and J. A. Moore. 1971. Teratology studies with 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicol. Appl. Pharmacol.* 20:396-403.

- Green, S. 1977. Cytogenetic effects of TCDD on rat bone marrow cells. *FDA By-Lines* 7(6):292.
- Hussain, S., L. Ehrenberg, G. Lofroth, and T. Gejvall. 1972. Mutagenic effects of TCDD on bacterial systems. *Ambio* 1 (1):32-33.
- Poland, A. and A. Kende. 1976. 2,3,7,8-Tetrochlorodibenzo-p-dioxin: environmental contaminant and molecular probe. *Fed. Proc.* 35(12):2404-2411.
- Poland, A., W. Greenlee, and A. Kende, 1979. Studies on the mechanism of action of the chlorinated dibenzo-p-dioxins and related compounds. P. 214-230. In *Health Effects of Halogenated Aromatic Hydrocarbons*. The New York Academy of Science.
- Vos, J. G. and J. A. Moore. 1974. Suppression of cellular immunity in rats and mice by maternal treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Int. Arch. Allergy* 47:777-794.
- Wasson, J. S., J. E. Huff and N. Loprieno. 1977/1978. A review of the genetic toxicology of chlorinated dibenzo-p-dioxin. *Mutation Research* 47:141-160.

G. DETECTION OF DIOXIN INDUCED DNA ABERRATIONS

- Buckton, K. E., W. M. C. Brown and P. G. Smith. 1967. Lymphocyte survival in men treated with X-rays for ankylosing spondylitis. *Nature* 214:270-272.
- Czeizel, E. and J. Kiraly. 1976. Chromosome examinations in workers producing klorinol and buvinol. P. 239-256. In *The Development of a Pesticide as a Complex Scientific Task*. L. Banki (Ed). Medicina (Budapest).
- Green, S. and F. S. Moreland. 1975. Cytogenetic evaluation of several dioxins in the rat. *Toxicol. Appl. Pharmacol.* 33(1):161.
- Hay, A. 1977. Identifying carcinogens. *Nature* 269:468-470.
- Hay, A. 1978. Vietnam's dioxin problem. *Nature* 271:597-598.
- Tenchini, M. L., R. Giorgi, C. Crimauco, G. Simoni, F. Nuzzo, and L. de Carli. 1977. Approaches to examination of genetic damage after a major hazard in chemical industry: preliminary cytogenetic findings in TCDD exposed subjects after Seveso accident. Presentation at the Expert Conference on Genetic Damage Caused by Environmental Factors, Oslo, Norway, May 11-13, 1977.

H. ANIMAL STUDIES

- Allen, J. R., D. A. Barsotti, J. P. Van Miller, L. J. Abrahamson and J. J. Lalich. 1977. Morphological changes in monkeys consuming a diet containing low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Food Cosmet. Toxicol. 15:401-410.
- Kociba, R. J., D. G. Keyes, J. E. Beyer, R. M. Carreon, C. E. Wade, D. A. Dittenber, R. P. Kalmins, L. E. Frauson, C. N. Park., S. D. Barnard, R. A. Hummel and C. G. Humiston. 1978. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats Toxicol. Appl. Pharmacol. 46:279-303.
- Kociba, R. J., D. G. Keyes, R. W. Lisowe, R. P. Kalmins, D. D. Dittenbar, C. E. Wade, S. J. Gorzinski, N. H. Mahle and B. A. Schwetz. 1979. Results of a two-year chronic toxicity and oncogenic study of rats ingesting diets containing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T.) Food Cosmet. Toxicol. (In Press.)
- Lamb, J., J. Moore, and T. Marks, 1980. Reproduction and fertility in treated male mice and evaluation of congenital malformations in their offspring. Congressional Record, August 6, 1980. P. S10904-11.
- McConnell, E. E., J. A. Moore and D. W. Dalgard. 1978. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rhesus monkeys (*Macaca mulatta*) following a single oral dose. Toxicol. Appl. Pharmacol. 43:175-187.
- McNulty, W.P. 1977. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin for rhesus monkeys: brief report. Bull. Environ. Contam. Toxicol. 18:108-109.
- Rowe, V. K. and T. A. Hymas. 1954. Summary of toxicological information on 2,4-D and 2,4,5-T type herbicides and an evaluation of the hazards to livestock associated with their use. Am. J. Vet. Res. 15:622-629.
- Schantz, S.L., D. A. Barsotti, and J.R. Allen. 1979. Toxicological effects produced in non-human primates chronically exposed to 50 ppt 2,3,7,8-tetrachlorodibenzo-p-dioxin. Presented at Meetings of Society of Toxicology, New Orleans, March 15, 1979.

I. CASE STUDIES

- Berkley, M. C. and K. R. Magee. 1963. Neuropathy following exposure to a dimethylamine salt of 2,4-D. Arch. Intern. Med. 111:351-353
- Bleiberg, J., M. Wallen, R. Brodtkin, and I. L. Applebaum. 1964. Industrially acquired porphyria. Arch. Dermatol. 89:793-797.

- Brandt, M. P. 1971. Herbatoxforgiftning, en Kort oversigt og et nyt tilfælde. (Herbatox poisoning, a brief review and a report of a new case). Ugeskrift for Læger 133:500-503. (Danish).
- Crow, K. 1978. Chloracne: the chemical disease. New Scientist 78-80.
- Jirasek, L., J. Kalensky, and K. Kubec. 1973. Acne chlorina a porphyria cutanea tarda pri vyrobe herbicid. (Acne chlorina and porphyria cutanea tarda during the manufacture of herbicides. Part I.) Ceskoslovenska Dermatologie 48(5):305-317.
- Jirasek, L., J. Kalensky, K. Kubec, J. Pazderova and E. Lukas. 1974. Acne chlorina, porphyria cutanea tarda a jine projevy celkove intoxikace pri vyrobe herbicid. (Acne chlorina, porphyria cutanea tarda and other manifestations of general intoxication during the manufacture of herbicides, Part II.) Ceskoslovenska Dermatologie 49(3):145-157.
- Oliver, R. M. 1975. Toxic effects of 2,3,7,8 tetrachloro-dibenzo-1,4-dioxin in laboratory workers. Br. J. Ind. Med. 32:49-53.
- Taylor, J., 1979. Environmental chloracne; update and overview. P. 295-307. In Health Effects of Halogenated Aromatic Hydrocarbons. The New York Academy of Science.

J. EPIDEMIOLOGIC STUDIES

- Alfred, J. E. (Chairman). September 1978. Report on the consultative council on congenital abnormalities in the Yarram District (Australia). Australian Commission on Public Health. Document No. 47-12004/78, Government Printing Office, Melbourne, Australia. 55p.
- Axelsson, O., and L. Sundell, 1974. Herbicide exposure, mortality and tumor incidence. An investigation on Swedish railroad workers. Scan J. Work, Environ, and Health. 11 (1974) 21-28.
- Axelsson, O., and L. Sundell, K. Anderson, C. Edling, C. Hogstedt, and H. Kling, 1980. Herbicide exposure and tumor mortality: an updated epidemiologic investigation on Swedish railroad workers. Manuscript.
- Cook, R. R., and K. M. Bodner, 28 October 1981. Dioxin and reproductive effects. International Symposium on Dioxins and Related Compounds, Arlington, Virginia.
- Eriksson, M., L. Hardell, N. Berg, T. Moller, and O. Axelsson, 1979. Case-control study on malignant mesenchymal tumors of the soft tissue and exposure to chemical substances. Lakartidningen 76: 3872-72 (Swedish).
- Hardell, L., and A. Sandstrom, 1979. Case-control study: soft tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. British Journal of Cancer, 39: 711-717.

- Hardell, L., M. Eriksson, and P. Lenner, 1980. Malignant lymphoma and exposure to chemical substances, especially organic solvents, chlorophenols and phenoxyacids. *Lakartidningen* 77(4): 208-210 (Swedish).
- Homburger, E., G. Reggiani, J. Sambeth and H. Wipf. 1979. The Seveso accident: its nature, extent and consequences. Givaudan Research Co. Ltd. and F. Hoffman-LaRoche and Co. Ltd., 4002 Basle, Switzerland. Mim. Unpublished data, 80 p.
- Kramer, C. G. 1977, Revised 1974. Health of employees exposed to 2,4,5-T. Dow Chemical Co., Midland, Michigan. Mim. Unpublished data, 19 p.
- Lavy, Terry L., Scott Shepard, and John D. Mattice, 1980. Exposure Measurements of Applicators Spraying (2,4,5-Trichlorophenoxy) and acetic Acid in the Forest. *J. Agric. Food Chem* 28:626-630.
- Pocchiari, F., Silano, V., Zampier, A. 1979. Human health effects from accidental release of tetrachlorodibenzo-p-dioxin (TCDD) at Seveso, Italy. *Ann. N.Y. Acad. Sci.*, p. 311-320.
- Poland, A. P., D. Smith, G. Metter and P. Possick. 1971. A health survey of workers in a 2,4-D and 2,4,5-T plant. *Arch. Environ. Health* 22(3): 316-327.
- Regianni, G., 1980. Acute human exposure to TCDD in Seveso, Italy. *J. Toxicology and Environmental Health*, 6: 27-43.
- Smith, A. H. 28 October 1981. (Personal communication), International Symposium on Chlorinated Dioxins and Related Compounds, Arlington, Virginia.
- Theiss, A., and R. Frentzel-Beyme, 1977. Mortality study of persons exposed to dioxin following an accident which occurred in the BASF on November 13, 1953. Presented at the Fifth International Conference of Medichem, San Francisco, California, September 1977.
- Tung, T. T. 1973. Le Cancer primaire du foie au Vietnam. (Primary cancer of the liver in Vietnam.) *Chirurgie* 99(7):427-36. (French).
- Zack, J., and R. Suskind, 1980. The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident. *J. Occupational Medicine* 22(1): 11-14.
- Report of Assessment of a Field Investigation of Six-year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Spray Practices. Epidemiologic Studies Program, Human Effects Monitoring Branch, Environmental Protection Agency, Washington, DC, February 29, 1979. Mim. Unpublished data, 100 p.

K. STATISTICAL REFERENCES

- Armitage, P. 1971. Further analysis of qualitative data. P 384-391. In Statistical Methods in Medical Research. John Wiley and Sons, New York
- Bishop, Y. M. M., S. E. Fienberg, and P. W. Holland. 1975. Models for three-dimension arrays. P 31-42. In Discrete Multivariate Analysis: Theory and Practice. The MIT Press, Mass.
- Breslow, N. 1970. A generalized Kruskal-Wallis test for comparing k samples subject to unequal patterns of censorship. Biometrika 57:579-594.
- Breslow, N. E., and J. Crowley. A large sample study of the life table and product limit estimates under random censorship. Ann. Stat. 2:437-453.
- Breslow, N. E. and N. E. Day. 1975. Indirect Standardization and multiplicative models for rates, with reference to the age adjustment of cancer incidence and relative frequency data. J. Chron. Dis. 28:289-303.
- Breslow, N. E. 1975. Analysis of survival data under the proportional hazards model. Int. Stat. Rev. 43: 45-58.
- Carpenter, R. G. 1977. Matching when covariables are normally distributed. Biometrika 64:299-307.
- Chiang, C. L. 1968. Chapters 9-12, P 189-296. In Introduction to stochastic processes ... biostatistics. John Wiley and Sons, New York.
- Copeland, K. T., M. Checkoway, A. J. McMichael, and R. H. Holbrook. 1977. Bias due to misclassification in the estimation of relative risk. Am. J. Epi. 105:488-495.
- Cox, D. R. 1958. The regression analysis of binary sequences. J. R. Statist. Soc. -B. 20:215-232.
- Cox, D. R. 1958. Two further applications of a model for binary regression. Biometrika 45:562-565.
- Cox, D. R. 1966. A simple example of a comparison involving quantal data. Biometrika 53: 215-220.
- Cox, D. R. 1972. Regression methods and life tables. J. R. Statist. Soc. -B 34:087-220.
- Fleiss, J. L. 1973. Analysis of data from matched samples. P 11-80. In Statistical Methods For Rates and Proportions. John Wiley and Sons, New York.
- Frank, J. 1977. Survival analysis with time-dependent covariates. Ph.D. Thesis, University of California, Berkeley, California.

- Gehan, E. 1965b. A generalized two-sample Wilcoxin test for doubly censored data. *Biometrika* 52:650-653.
- Gehan, E. 1965a. A generalized Wilcoxin test for comparing arbitrarily censored samples. *Biometrika* 52:203-223.
- Gross, A. and V. Clark. 1975. Chapter 2, P 23-48. In *Survival Distributions: Reliability Applications in the Biomedical Sciences*, John Wiley and Sons, New York.
- Holford, T., White, C., and Kelsey, J., 1978. Multi-variate analysis for matched case-control studies. *Am. J. Epi.* 107: 245-256.
- Kaplan, E. and P. Meier. 1958. Nonparametric estimation from incomplete observations. *J.A.S.A.* 53:457-581.
- Karger, S. 1972. Cardiovascular studies, P 298 In *Medical Primatology*, Part III. Basel, Munchen.
- Mantel, N. 1966. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports* 50:163-170.
- Mantel, N. 1967. Ranking procedures for arbitrarily restricted observations. *Biometrics* 23:65-78.
- McCullagh, P., 1978. A class of parametric models for the analysis of square contingency tables with ordered categories. *Biometrika* 65: 413-418.
- McKinlay, S. M. 1977. Pair-Matching: a reappraisal of a popular technique. *Biometrics* 33:725-735.
- McKinlay, S. M. 1975. The design and analysis of the observational study: a review. *J.A.S.A.* 70:503-520.
- Miettinen, O. S. 1969. Individual matching with multiple controls in the case of all-or-none response. *Biometrics* 25: 339-355.
- Miettinen, O. S. 1970. Matching and design efficiency in retrospective studies. *Am. J. Epi.* 91:111-117.
- Peto, R. and J. Peto. 1972. Asymptotically efficient rank invariant test procedures. *J. R. Statist. Soc. -A* 135:185-198.
- Peritz, E. and R. Ray. 1978. Some statistical methods for survival analysis with rare failure. *Comm. Stat.* A7:619-636.
- Schoenfeld, D., 1980. Chi-squared goodness of fit tests for the proportional hazards regression model. *Biometrika* 67: 145-153.

- Stuart, A., 1955. A test for promogeneity of the marginal distributions in a two-way classification. *Biometrika* 42: 412-416.
- Torrance, E. P. 1954. The development of a preliminary life experience inventory for the study of fighter interceptor pilot combat effectiveness. AFPTRC-TR-54-89. Air Force Personnel Training and Research Center, Lackland Air Force Base, Texas.
- Ury, H. K. 1975. Efficiency of case-control studies with multiple controls per case: continuous or dichotomous data. *Biometrics* 31:643-649.
- Walker, W. H. and D. B. Duncan. 1967. Estimation of the probability of an event as a function of several independent variables. *Biometrika* 54:167-179.
- Wei, L. J., 1980. A generalized Gehan and Gilbert test for paired observations which are subject to arbitrary right censorship. *J. Am. Statist. Assoc.*, to appear.
- Zuckerman, M. 1972. Manual and research report of the sensation seeking scale. Department of Psychology, University of Delaware, Newark, Delaware.

XV. APPENDIX

TABLE A-1	SUMMARY OF 2,4-D, 2,4,5-T AND TCDD ANIMAL STUDIES
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TABLE A-1

SUMMARY OF 2,4-D, 2,4,5-T, AND TCDD ANIMAL STUDIES

	<u>2,4-D</u>	<u>2,4,5-T</u>	<u>TCDD</u>
LD ₅₀ RANGE (ACUTE)	100-1000 mg/kg	100-1000 mg/kg	1-1000 g/kg
CHRONIC TOXIC DOSE	APPROACHES ACUTE LEVEL RAPID CLEARANCE	1/2 ACUTE LEVEL; VARIABLE CLEARANCE	MARKEDLY LOWER LEVEL BIOACCUMULATION
SIGNS OF ACUTE/ CHRONIC TOXICITY	ANOREXIA WEIGHT LOSS MUSCULAR WEAKNESS IRRITATED G.I. TRACT MINOR LIVER INJURY MINOR KIDNEY INJURY MINOR LUNG CONGESTION	ANOREXIA ATAXIA G.I. INJURY LIVER CONGESTION KIDNEY CONGESTION	WEIGHT LOSS INVOLUTION OF THYMUS ALOPECIA EPITHELIAL CHANGES LIVER LESIONS (VARIABLE) HYPOTHYROIDISM
EMBRYOTOXIC DOSE	APPROACHES TOXIC LEVEL	APPROACHES TOXIC LEVEL	MARKEDLY BELOW TOXIC MATERNAL LEVELS
TERATOGENICITY	QUESTIONABLE; WEAK AT BEST	*LOW INCIDENCE ONLY IN MICE (CLEFT PALATES DILATED RENAL PELVIS)	SPECIES VARIA- TIONS: YES MICE NO RATS
CARCINOGENICITY	QUESTIONABLE; WEAK AT BEST	ONE STUDY: YES NUMEROUS STUDIES: NO	EPITHELIAL CHANGES IN PRIMATES: YES IN RATS

TABLE A-2 "SYMPTOM COMPLEX" DERIVED FROM LITERATURE REVIEW OF CASE STUDIES
EXPOSED TO 2,4-D; 2,4,5-T AND/OR TCDD

<u>2,4-D</u>	<u>2,4,5-T (+ TCDD)</u>	<u>TCDD</u>
	CHLORACNE	CHLORACNE
	PORPHYRIA	PORPHYRIA
	HYPERPIGMENTATION	HYPERPIGMENTATION
ASTHENIA	ASTHENIA	ASTHENIA
PERIPHERAL NEUROPATHY	PERIPHERAL NEUROPATHY	PERIPHERAL NEUROPATHY
SWEATING/FEVER		
CARDIAC DISTURBANCE	CARDIAC DISTURBANCE	CARDIAC DISTURBANCE
RENAL DYSFUNCTION		RENAL DYSFUNCTION
LIVER DYSFUNCTION	LIVER DYSFUNCTION	LIVER DYSFUNCTION
GI DISTURBANCE	GI DISTURBANCE	GI DISTURBANCE
HEADACHE		
PNEUMONITIS		
GSE PROTEIN ABNORMALITIES		IMMUNOTOXICITY
CONVULSIONS		HEARING/SNELL DISTURBANCES

TABLE A-3 DETAILED LISTING OF SYMPTOMS/SIGNS BY MAJOR CATEGORY
FROM LITERATURE REVIEW OF CASE STUDIES EXPOSED TO 2,4-D; 2,4,5-T AND/OR TCDD

<u>NEURO-PSYCHIATRIC ABNORMALITIES</u>	
<u>AESTHETIA</u>	<u>PERIPHERAL NEUROPATHY</u>
ANXIETY	HYPOREFLEXIA
DEPRESSION	WEAKNESS
FATIGUE	PARESTHESIAS
APATHY	EXTREMITY NUMBNESS
LOSS OF DRIVE	MYALGIA
DECREASED LIBIDO	GAIT DISTURANCE
IMPOTENCY	"MILD" PARESIS
SLEEPLESSNESS	
EMOTIONAL INSTABILITY	
ANOREXIA	
DIZZINESS	
DECREASED LEARNING ABILITY	

TABLE A-3 (CONTINUED) DETAILED LISTING OF SYMPTOMS/SIGNS BY MAJOR CATEGORY
FROM LITERATURE REVIEW OF CASE STUDIES EXPOSED TO 2,4-D, 2,4,5-T AND/OR TCDD

DERMATOLOGIC DISEASE

CHLORACNE
PORPHYRIA CUTANEA TARDA
HYPERPIGMENTATION
HIRSUTISM (BODY)
ALOPECIA OF THE SCALP

OTHER DISORDERS

HEPATIC DYSFUNCTION

INCREASED CHOLESTEROL
AND TRIGLYCERIDE
INCREASES IN LIVER
FUNCTIONAL TESTS

RENAL DYSFUNCTION

PROTEINURIA
DECREASED OUTPUT
TUBULAR DEGENERATION
GLOMERULAR DEGENERATION
RENAL GLUCOSURIA

GI DISTURBANCE

NAUSEA
VOMITING
DIARRHEA
GASTRITIS
ABDOMINAL PAIN

CARDIAC DISTURBANCE

BRADYCARDIA
TACHYCARDIA
ATRIAL FIBRILLATION

TABLE A-4
AGE COMPARISON OF EXPOSED SUBJECTS AND THEIR MATCHED CONTROLS

AFSC/Race Strata	Number of Exposed Subjects	Mean Number of Matched Controls	Age Difference Range
Officer: Pilot/Caucasian /Black	349 6	9.5 2.7	0-60 0-57
Nonpilot/Caucasian /Black	78 2	10.0 10.0	0-07 0-36
Other/Caucasian /Black	25 1	10.0 5.0	0-27 0-54
Enlisted: Flying/Caucasian /Black	187 15	10.0 9.8	0-35 0-58
Nonflying/Caucasian /Black	528 51	10.0 10.0	0-48 0-06
Killed in Action			
Officers/Caucasian /Black	14 1	-- --	-- --
Enlisted/Caucasian /Black	7 0	-- --	-- --

TABLE A-5
STATISTICAL DESCRIPTION OF THE MATCHING PROCESS

DIST IN MONTHS	COUNT	DIST IN MONTHS	COUNT	ABSOLUTE DIST IN MONTHS	COUNT	%	CUMULATIVE TOTAL	%
- 1	847	1	828	0	8612	70.6	8612	70.6
- 2	231	2	231	1	1675	13.7	10287	84.3
- 3	114	3	121	2	462	3.8	10749	88.1
- 4	92	4	91	3	235	1.9	10984	90.1
- 5	88	5	67	4	183	1.5	11167	91.6
- 6	41	6	47	5	155	1.3	11322	92.8
- 7	33	7	39	6	88	0.7	11410	93.5
- 8	28	8	22	7	72	0.6	11482	94.1
- 9	27	9	23	8	50	0.4	11532	94.5
-10	10	10	21	9	50	0.4	11582	95.0
-11	18	11	18	10	31	0.3	11613	95.2
-12	17	12	22	11	36	0.3	11649	95.5
-13	9	13	18	12	39	0.3	11688	95.8
-14	23	14	11	13	27	0.2	11715	96.0
-15	11	15	8	14	34	0.3	11749	96.3
-16	20	16	15	15	19	0.2	11768	96.5
-17	16	17	11	16	35	0.3	11803	96.8
-18	4	18	6	17	27	0.2	11830	97.0
-19	6	19	6	18	10	0.1	11840	97.1
-20	11	20	3	19	12	0.1	11852	97.2
-21	10	21	9	20	14	0.1	11866	97.3
-22	4	22	6	21	19	0.2	11885	97.4
-23	4	23	13	22	10	0.1	11895	97.5
-24	4	24	5	23	17	0.1	11912	97.7
-25	3	25	4	24	9	0.1	11921	97.7
-26	6	26	7	25	7	0.1	11928	97.8
-27	2	27	8	26	13	0.1	11941	97.9
-28	6	28	8	27	10	0.1	11951	98.0
-29	2	29	9	28	44	0.1	11965	98.1
-30	2	30	4	29	11	0.1	11976	98.2
-31	2	31	5	30	6	0.0	11982	98.2
-32	1	32	5	31	7	0.1	11989	98.3
-33	6	33	2	32	6	0.0	11995	98.3
-34	3	34	3	33	8	0.1	12003	98.4
-35	5	35	7	34	6	0.0	12009	98.5
-36	4	36	3	35	12	0.1	12021	98.6
-37	3	37	3	36	7	0.1	12028	98.6
-38	4	38	11	37	6	0.0	12034	98.7
-39	2	39	5	38	15	0.1	12049	99.8
-40	3	40	5	39	7	0.1	12056	99.8
-41	5	41	2	40	8	0.1	12064	99.9
-42	4	42	6	41	7	0.1	12071	99.0
-43	2	43	2	42	10	0.1	12081	99.0
-44	6	44	9	43	4	0.0	12085	99.1
-45	9	45	4	44	15	0.1	12100	99.2
-46	3	46	6	45	13	0.1	12113	99.3
-47	0	47	4	46	9	0.1	12122	99.4
-48	0	48	3	47	4	0.0	12126	99.4
-49	3	49	1	48	3	0.0	12129	99.4
-50	4	50	4	49	4	0.0	12133	99.5
-51	2	51	2	50	8	0.1	12141	99.5
-52	0	52	0	51	4	0.0	12145	99.6
-53	4	53	4	52	0	0.0	12145	99.6
-54	6	54	2	53	8	0.1	12153	99.6
-55	3	55	3	54	8	0.1	12161	99.7
-56	4	56	0	55	6	0.0	12167	99.8
-57	3	57	2	56	4	0.0	12171	99.8
-58	5	58	3	57	5	0.0	12176	99.8
-59	5	59	1	58	8	0.1	12184	99.9
-60	3	60	4	59	6	0.0	12190	99.9
				60	7	0.1	12197	100.0

Table A-6
SPECIFIC RULES FOR ENTRY INTO THE MORBIDITY STUDY

<u>CIRCUMSTANCES</u>	<u>RULES</u>
RANCH HANDER (RH) DIES FOLLOWING INITIAL DATA COLLECTION	CONTROL FOLLOWED THROUGHOUT AND REPLACED AS NECESSARY
RH DIES OF COMBAT CAUSE	MEDICAL RECORDS REVIEWED; NO CONTROL SET FORMED
RH DIES OF NONCOMBAT CAUSE PRIOR TO INITIAL DATA COLLECTION	1ST ORDER SURROGATE INTERVIEW ACCOMPLISHED; CONTROL SELECTED AND FOLLOWED THROUGHOUT; AS NECESSARY
RH NONCOMPLIANT FOR BASELINE QUESTIONNAIRE AND PHYSICAL	CONTROL FOLLOWED THROUGHOUT THE STUDY; REPLACED AS NECESSARY
RH COMPLIANT FOR QUESTIONNAIRE; NONCOMPLIANT FOR BASELINE PHYSICAL EXAMINATION	CONTROL FOLLOWED THROUGHOUT THE STUDY; REPLACED AS NECESSARY
RH NONCOMPLIANT DURING FOLLOWUP	CONTROL FOLLOWED THOUGHOUT THE STUDY; REPLACED AS NECESSARY
CONTROL DIES FOLLOWING INITIAL DATA COLLECTION	NOT REPLACED IN THE PROSPECTIVE STUDY OF MORBIDITY
CONTROL DIES OF COMBAT CAUSE	MEDICAL RECORDS REVIEWED; EXCLUDED FROM FURTHER STUDY
CONTROL DIES OF NONCOMBAT CAUSE PRIOR TO INITIAL DATA COLLECTION	INCLUDED IN MORTALITY AND RETROS- PECTIVE MORBIDITY STUDIES; SUR- ROGATE INTERVIEW ACCOMPLISHED. NOT INCLUDED IN PROSPECTIVE MORBIDITY STUDY AND REPLACED BY A LIVING COMPLIANT CONTROL.
CONTROL NONCOMPLIANT FOR BASELINE PHYSICAL EXAMINATION	CONTROL FOLLOWED THROUGHOUT STUDY REPLACE AS NECESSARY
CONTROL NONCOMPLIANT DURING FOLLOWUP	CONTROL FOLLOWED THROUGHOUT STUDY REPLACE AS NECESSARY
NONCOMPLIANT CONTROL RETURNS TO STUDY	BOTH PRIMARY AND REPLACEMENT CONTROLS WILL BE CONTINUED IN STUDY

Table A-7
SCHEDULE AND MODE OF CONTACTS WITH
STUDY SUBJECTS

<u>STUDY PHASE</u>	<u>CONTACT MADE</u>	<u>TIME</u>
Morbidity Study	Introductory Letters	Oct 81
Morbidity Study	Comprehensive Questionnaire	Oct 81-Mar 82
	Baseline Physical Exam	Dec 81-Sep 82
Follow-up Study	Adaptive Questionnaire	Oct 83-Mar 84
	Adaptive Physical Examination	Dec 84-Jun 85
	Adaptive Questionnaire	Oct 86-Mar 87
	Adaptive Physical Examination	Dec 86-Jun 87
	Adaptive Questionnaire	Oct 91-Mar 92
	Adaptive Physical Examination	Dec 91-Jun 92
	Adaptive Questionnaire	Oct 96-Mar 97
	Adaptive Physical Examination	Dec 96-Jun 97
	Adaptive Questionnaire	Oct 2001-Mar 2002
	Adaptive Physical Examination	Dec 2001-Jun 2002

Table A-8
MONTE CARLO SIMULATION

PROGRAM

```

10 DIM C(10,3)
20 DIM A(10,3)
30 P2=.25
40 D1=.45
50 M=0
60 N=0
70 FOR I=1 TO 10
80 FOR J=1 TO 3
90 A(I,J)=0
100 C(I,J)=0
110 NEXT J
120 NEXT I
130 M=M+1
140 PRINT M
150 IF M=1001 THEN 330
160 F=1
170 I=1
180 J=1
190 C(I,J)=RND(1)
200 X=P2+F*D1

210 IF C(I,J) > X THEN 270
220 I=I+1: F=1
230 IF I > 10 THEN 250
240 GOTO 190
250 N=N+1
260 GOTO 130
270 A(I,J)=A(I,J)+1
280 J=J+1
290 IF J>3 THEN 320
300 F=0
310 GOTO 190
320 GOTO 130
330 STOP
340 SELECT PRINT 215
350 FOR I=1 TO 10
360 PRINT A(I,1), A(I,2),
370 NEXT I
380 PRINT
390 PRINT "N(1)", N(1)
400 PRINT "N(2)", N(2)
410 PRINT "N(3)", N(3)
420 END

```

GLOSSARY

I = Control individual index

J = Examination number index

A(I,J) = Attendance array = number of times the ith control was used for the jth examination

C(I,J) = Testing variable array

N = number of times no control was available

M = number of matches attempted

$\left. \begin{array}{l} D1 \\ P2 \end{array} \right\} = \text{preselected probabilities. } P_1 = D1 + P2 \text{ and } P_2 = P2$

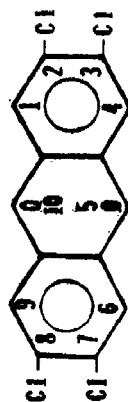
RND = Random

DIM = Dimension

F = Flag

Figure A-1

2, 3, 7, 8-TETRACHLORODIBENZO-p-DIOXIN (TCDD)



- MOLECULAR WEIGHT 321.8935
- MELTING POINT 303-305°C
- DECOMPOSITION POINT 980-1,000°C
- SOLUBILITY, GRAMS/LITER

ORTHO-DICHLOROBENZENE	1.40
CHLOROBENZENE	0.72
ORANGE HERBICIDE	0.58
BENZENE	0.57
CHLOROFORM	0.37
ACETONE	0.11
METHANOL	0.01
WATER	2×10^{-7}

ESTIMATED IDENTIFICATION/PARTICIPATION OF THE RANCH HAND POPULATION

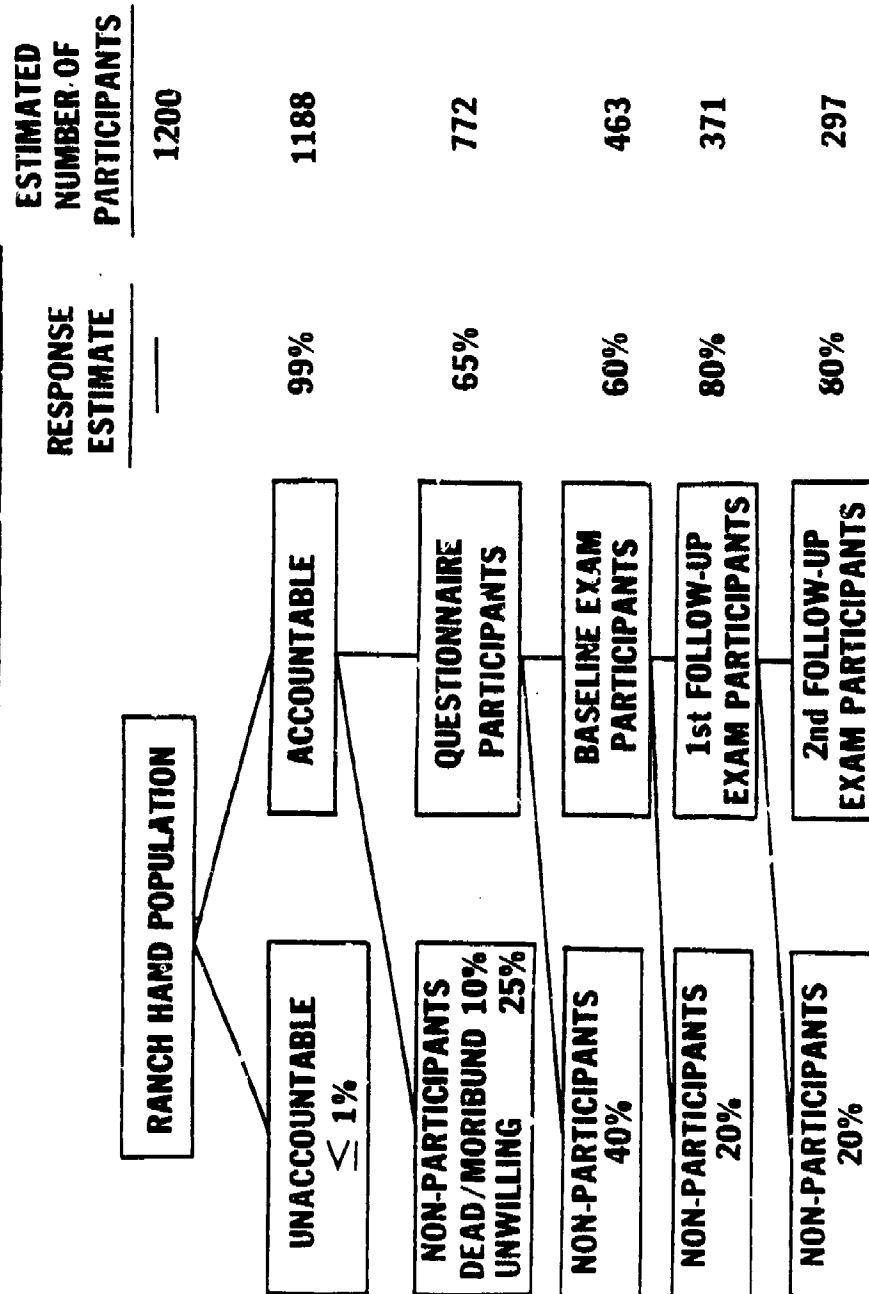
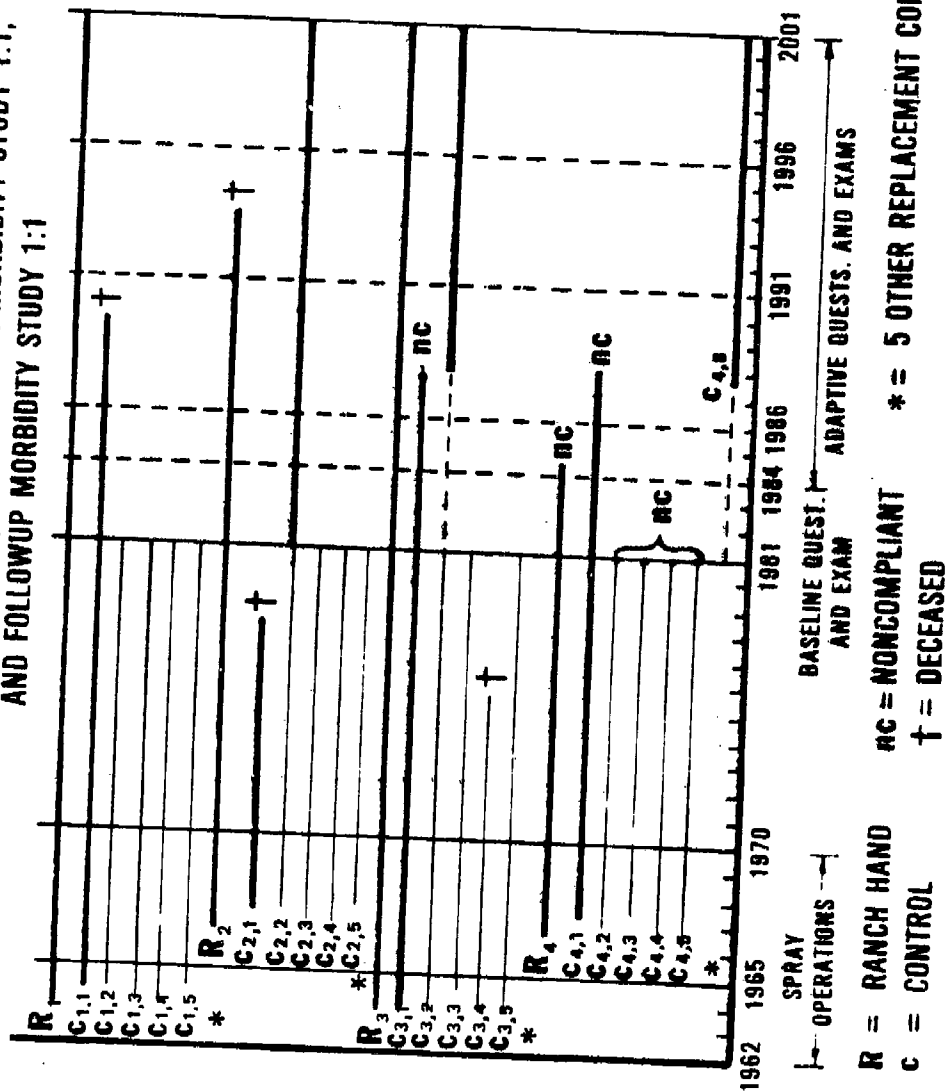


Figure A-2

Figure A-3

STUDY DESIGN FORMAT **MORTALITY STUDY 1:5, RETROSPECTIVE MORBIDITY STUDY 1:1,** **AND FOLLOWUP MORBIDITY STUDY 1:1**



XVI. Examiner's Handbook

A. General Instructions

Project RANCH HAND II is a multiyear effort to determine whether or not C-123 aircrew members who were engaged in the aerial spraying of herbicides in Vietnam have developed significant adverse health effects from that exposure. Detailed surveys of the world's literature have been used in designing the history questionnaires, physical examination protocol, and laboratory procedures.

This phase of Project RANCH HAND II involves a cross sectional study of the subject's health at the time of examination. It is important that examiners remain unaware of the subject's status as a RANCH HAND participant or as a control subject. The physician examiner is tasked to examine and objectively record his findings. The examining physician is not, and cannot be expected to arrive at any definitive diagnosis as the full history and laboratory results will not be available to him. Medical history, laboratory results and physical examination findings will be evaluated by an independent diagnostician employed by the contractor. This diagnostician will formulate diagnoses and differential diagnoses, if appropriate. Additional procedures to treat or evaluate emergency or urgent medical conditions will be directed only by this physician. In addition, he will present a detailed analysis and debriefing to the study subject and provide a copy of the analysis to the subject's personal physician, if so requested.

The physicians performing examinations for Project RANCH HAND II should be aware that the report of examination will become a permanent record. This report will be referred to not only in the near future as the cross sectional study is analyzed, but also at the time of the next review of the subject in the follow-up phases of Project RANCH HAND. These examinations will define the health status of the subjects at a point in time, and will establish the presence or absence of abnormal physical findings. After statistical review of the study groups, these findings may permit definition of a chronic effect due to exposure. An inaccurate examination may lead to falacious study results in two ways: a presumed syndrome may be defined which does not in fact exist, or a syndrome which in fact exists may not be defined with enough validity to warrant further actions.

The examining physician is responsible for recording a complete and detailed report of the physical examination. In this role, the examining physician is tasked with collecting evidence of the presence or absence of physical signs of abnormality only. The formulation of diagnostic impressions by individual examiners is not requested nor desired. All items on the physical examination report form must be completed. It is imperative that the physician make such additional remarks as may be required to adequately describe existing physical and mental impairments. Since clinical endpoints have not been well defined following chronic exposure to Herbicide Orange, the examining physician and the diagnostician must not definitively ascribe abnormalities to herbicide exposure during the course of the examination or during the patient's debriefing. If, during the examination, the physician

discovers evidence of acute serious illness requiring immediate treatment, the normal emergency or urgent care procedures of the medical facility would apply. Such care will be supplied at Air Force expense. If during the examination, there is evidence of illness requiring non-emergency medical attention, the diagnostician should inform the subject and offer to forward or have forwarded pertinent information to the subject's physician. A clear record of any such advice and treatment should be recorded. The ultimate value of the RANCH HAND II Study will lie in the collection of complete, accurate and, whenever possible, quantitative data permitting the most stringent and powerful statistical analysis. For that reason, the physical examination protocol requires exact measurements in many instances, and the use of defined meanings of semiquantitative indicators in other places.

B. Conduct of the Examination

(1) Upon arrival at the examining facility, the subject should be briefed by the on-site monitor on the appointments which have been arranged, their times, and locations.

(2) Collation and forwarding of examination results

The monitor will complete a checklist for each study subject and review all medical information for quality and completeness before forwarding to USAFSAM/EK, Brooks AFB, TX 78235.

C. Examination Format

SECTION	PHYSICAL EXAMINATION	SUBJECT NUMBER
1. GENERAL APPEARANCE		
a. Appearance/Stated Age ☐ Younger Than ☐ Older Than ☐ Same As b. ☐ Well-nourished ☐ Obese ☐ Under-nourished ☐ Older Than c. Appearance of illness or distress ☐ Yes ☐ No d. Hair Distribution ☐ Normal ☐ Abnormal e. Temperature _____ SPECIFY: _____		
2. HEIGHT cm	WEIGHT (Undressed) kg	SITTING BLOOD PRESSURE RIGHT ARM AT HEART LEVEL SYSTOLIC _____ DIASTOLIC _____
3. PULSE RATE _____ REGULAR: ☐ YES ☐ NO Describe any irregularities.		
a. Irregular ☐ b. Irregularly irregular ☐ c. VPBs per minute _____		
4. EYE GROUND ☐ NORMAL ☐ ABNORMAL Describe any vascular lesions, hemorrhages, exudates.		
☐ A-V nicking ☐ Hemorrhages papilledema ☐ ↑ light reflex ☐ Exudates ☐ Papilledema ☐ Arteriolar spasm ☐ Disk Pallor ☐ ↑ Cupping		
5. ARCUS SENILIS ☐ PRESENT ☐ ABSENT 5a. Abnormal Ocular Pigmentation ☐ Yes ☐ No		
6. ENT ☐ NORMAL ☐ ABNORMAL Describe any abnormality.		
Tympanic membranes intact ☐ Yes ☐ No R ☐ L Nasal ulcerations ☐ No ☐ Yes		
7. NECK (Especially thyroid gland) ☐ NORMAL ☐ ABNORMAL Describe any abnormality.		
Thyroid gland palpable ☐ Enlarged ☐ Parotid gland enlargement ☐ Nodules ☐ R ☐ L Tenderness ☐ Carotid pulses _____		
8. THORAX AND LUNGS ☐ NORMAL ☐ ABNORMAL Describe any abnormality, especially basilar rales.		
☐ Asymmetrical expansion ☐ Wheezes Circumference at nipple level ☐ Hyperresonance ☐ Rales Expiration _____ cm ☐ Dullness Inspiration _____ cm		
9. HEART ☐ NORMAL ☐ ABNORMAL Describe any enlargement, irregularity of rate, murmurs, or thrills.		
Displacement of apical impulse ☐ No ☐ Yes Precordial thrust ☐ No ☐ Yes Heart sounds normal ☐ Yes ☐ No ☐ S1 ☐ S2 ☐ S3 ☐ S4		
(Continued in Item 18 on Reverse)		
10. ABDOMEN ☐ NORMAL ☐ ABNORMAL Describe any abnormality with special attention to the spleen and liver. Record waist measurement on attached form.		
☐ Hepatomegaly ☐ Other mass - Specify: _____ cm Liver Span ☐ Splenomegaly ☐ Tenderness ☐ Liver ☐ Spleen ☐ Other, specify: _____		
11. EXTREMITIES ☐ NORMAL ☐ ABNORMAL Describe any edema or signs of vascular insufficiency.		
☐ Absence, specify: ☐ Edema ☐ Clubbing of nails ☐ Pitting ☐ Non-pitting ☐ Varicosities ☐ Loss of hair on toes ☐ R ☐ L		

SECTION		PHYSICAL EXAMINATION (Continued)				
12. PERIPHERAL PULSES		NORMAL	DIMIN.	ABSENT	COMMENTS	
RADIAL						
FEMORAL						
POPLITEAL						
DORSALIS PEDIS						
POSTERIOR TIBIAL						
13. SKIN		☐ NORMAL	☐ ABNORMAL			Indicate type and location of lesions on the attached anatomical figure
☐ Dermatographia						
☐ Comedones		☐ Hyperpigmentation				☐ Palmar Keratosis
☐ Acneiform lesions		☐ Jaundice				☐ Petechiae
☐ Acneiform scars		☐ Spider angiomas				☐ Ecchymoses
☐ Depigmentation		☐ Palmar erythema				☐ Soles of feet
☐ Inclusion cysts		Full-Face and Bilateral profile photos taken				☐ Nails ☐ Biopsy Taken
☐ Cutis Rhomboidalis						☐ Yes ☐ No ☒ Yes ☐ No
14. MUSCULOSKELETAL		☐ NORMAL	☐ ABNORMAL			
☐ Muscle - Specify:		☐ Spine				
☐ Weakness		☐ Scoliosis				
☐ Tenderness		☐ Kyphosis				
☐ Abnormal Consistency		☐ Tenderness, Level				
☐ Atrophy		☐ Decreased range of motion				☐ Pelvic tilt
						☒ Straight Leg Raising: Right/Left
15. GENITOURINARY - RECTAL - MENEA		☐ NORMAL	☐ ABNORMAL			
☐ Inguinal hernia		☐ R	☐ L			
☐ Testes		Absent Enlarged Atrophic		☐ Varicocele	☐ Hemorrhoids	
☐ R		☐	☐	☐ Epididymis	☐ Prostatic Enlargement	
☐ L		☐	☐	☐ Scrotal Mass	☐ Rectal mass	
				cm dia		
16. LYMPH NODES - CHECK ALL AREAS.		☐ NORMAL	☐ ABNORMAL - SPECIFY CERVICAL, OCCIPITAL, SUPRACLAVICULAR, AXILLARY, EPITRACHEAL, INGUINAL, FEMORAL			
☐ Enlarged		☐	☐ Tender	☐ Hard	☐ Fixed ☐ Confluent	
17. NERVOUS SYSTEM - SEE ATTACHED FORMS						
18. HEART AND OTHER OBSERVATIONS						
(Continued from Item 9)						
Normal ☐ No ☐ Yes Area ☐ No ☐ Pn ☐ Apex						
Sys ☐						
Dia ☐						
DATE OF EXAMINATION						
MONTH DAY YEAR			TYPED OR PRINTED NAME OF EXAMINING PHYSICIAN			
EXAMINING FACILITY			SIGNATURE			

CLINICAL RECORD

NEUROLOGICAL EXAMINATION

HEAD AND NECK - Normal to Palpations/Inspection ☐ Y ☐ N Specify Scar ☐Asymmetry ☐ Depression ☐Carotid Bruit ☐ No ☐ R ☐ LNeck Range of Motion ☐ Normal or Decreased to ☐ Left ☐ Right☐ Forward ☐ Backward

TRUNK

MOTOR SYSTEM - Handedness Right ☐ Left ☐Gait ☐ Normal or ☐ Broad Based ☐ Ataxic ☐ Small Stepped ☐ Other-SpecifyAssociated Movements ☐ Arm Swing ☐ Normal or Abnormal ☐ R ☐ L

Muscle Status (strength, tone, volume, tenderness, fibrillations)

Bulk ☐ Normal ☐ AbnormalTone Upper Extremities ☐ Normal or ☐ Increased ☐ Decreased☐ Right ☐ LeftLower Extremities ☐ Normal or ☐ Increased ☐ Decreased☐ Right ☐ LeftStrength - Distal wrist extensors ☐ Normal ☐ DecreasedAnkle/Toe Dors/Flexors ☐ Normal ☐ Decreased ☐ R ☐ LProximal Deltoids ☐ Normal ☐ Decreased ☐ R ☐ LHip Flexors ☐ Normal ☐ Decreased ☐ R ☐ LAbnormal Movements (tremors, tics, choreas, etc.) Fasciculations ☐ No ☐ Yes (1-4+)Tenderness ☐ No ☐ Yes (1-4+)Tremor ☐ No ☐ Yes - SpecifyUpper Extremity ☐ R ☐ L ☐ Resting ☐ Essential ☐ IntentionLower Extremity ☐ R ☐ L ☐ Other

Coordination (a) Equilibratory - Eyes Open

Eyes Closed - Romberg ☐ Positive (Abnormal) ☐ Negative (Normal)

Right Foot

Left Foot

(b) Nonequilibratory (F to N; F to F; H to K) Finger-to-nose-to-finger

☐ Normal ☐ Abnormal ☐ Right ☐ Left ☐ BothHeel-Knee-Shin ☐ Normal ☐ Abnormal ☐ Right ☐ Left ☐ Both

(c) Succession Movements (including check, rebound, posture-holding)

If indicated, check ☐ Normal ☐ Abnormal ☐ R ☐ LRapidly alternative movements ☐ Normal ☐ Abnormal ☐ R ☐ L ☐ Both

Skilled Acts

(a) Handwriting. If indicated, ☐ Normal ☐ Abnormal(b) Speech (articulation, aphasia, agnosia) Grossly ☐ Normal☐ Abnormal - Specify Dysarthria ☐Aphasia ☐

Reflexes (0-absent; 1-sluggish; 2-active; 3-very active; 4-transient clonus; 5-sustained clonus)

Deep	R	L	Deep	R	L	Other	R	L	Abnormal	R	L
									Babinski		
Biceps			Patellar			Cremasteric					
Triceps			Achilles								
Remarks											

MENINGEAL IRRITATION

☐ R ☐ L ☐ Both

Straight Leg Raising ☐ Normal ☐ Abnormal ☐ R ☐ L ☐ Both

NERVE STATUS (tenderness, tumors, etc.)

SENSORY SYSTEM (tactile, pain, vibration, position; If positive sensory signs are present, summarize below and indicate details on Anatomical Figure, Std. Form 53T)

Light Touch ☐ Normal ☐ Abnormal

Pin Prick ☐ Normal ☐ Abnormal (Map on Anatomical Figure)

Vibration (at ankle, 128 Hz tuning fork): ☐ Normal ☐ Abnormal ☐ R ☐ L ☐ Both

Position (Great toe): ☐ Normal ☐ Abnormal ☐ R ☐ L ☐ Both

CRANIAL NERVES

I R Smell ☐ Present ☐ Absent

L Smell ☐ Present ☐ Absent

II Fundus R Normal ☐ Abnormal ☐ Disk Pallor/atrophy
☐ Exudate ☐ Papilledema ☐ Hemorrhage

Fundus L Normal ☐ Abnormal ☐ Disk pallor/atrophy
☐ Exudate ☐ Papilledema ☐ Hemorrhage

Fields (to confrontation)

Right ☐ Normal ☐ Abnormal Left ☐ Normal ☐ Abnormal

III Normal ☐ Abnormal - Specify

IV Pupils-Size (mm) Equal ☐ Unequal ☐ Difference mm

VI Shape, position Round ☐ Other ☐ R ☐ L

Light Reaction Normal ☐ Abnormal ☐ R ☐ L

Position of Eyeballs

Movements R

L

Nystagmus Rotary ☐ Horizontal ☐ Vertical ☐
(Draw position)

XI

Ptosis R ☐ L ☐

V Motor R Clench Jaw - Symmetric ☐ Deviated ☐ R ☐ L ☐
L

Sensory R Normal ☐ Abnormal ☐ V₁ ☐ V₂ ☐ V₃ ☐
L Normal ☐ Abnormal ☐ V₁ ☐ V₂ ☐ V₃ ☐

Corneal Reflex R L

VII Motor R Normal smile ☐ Yes ☐ No Palpebral Fissure ☐ Yes ☐ No
L Normal smile ☐ Yes ☐ No Palpebral Fissure ☐ Yes ☐ No

IX Palate and Uvula

X Movement Normal ☐ Deviation to ☐ R ☐ L

Palatal Reflex R ☐ Normal ☐ Abnormal

L ☐ Normal ☐ Abnormal

XII Tongue-Protruded-Central ☐ R ☐ L ☐

Atrophy ☐ No ☐ Yes

MENTAL STATUS (alert, clear, cooperative, etc.) Gross abnormalities: ☐ No
☐ Yes - Specify

DIAGNOSTIC SUMMARY
SYNOPSIS OF POSITIVE FINDINGS

Medical History:

Physical Examination:

General

Dermatologic

Neurological

Psychological

Laboratory Results:

Diagnosis:

Differential Diagnosis, if applicable:

Date

Signature
of Diagnostician

D. Special Procedures

(1) Nerve Conduction Velocities

(a) These studies have been determined to be an important parameter in long-term follow-up studies of persons thought to have been exposed to Herbicide Orange components.

(b) The Nerve Conduction Velocities should be performed by a physician or by a specialty qualified technician under the supervision of a physician trained in neurophysiological methods.

(c) Specific NCVs (See form included in F. Below)

(1) Ulnar Nerve (one side only)

(a) motor (above elbow, below elbow)

(b) values recorded

(i) distal latency

(ii) NCV

(2) Peroneal Nerve (one side only)

(a) motor

(b) values recorded

(i) distal latency

(ii) NCV

(3) Sural Nerve (one side only)

(a) sensory: orthodromic

(b) values recorded: NCV

(d) Methods

PERONEAL NERVE

(1) Active electrode is placed over the extensor digitorum brevis and reference over the little toe. Stimulating electrodes are placed over anterior distal leg 8 cm proximal to active electrode. Proximal site is distal to head of fibula. If entrapment is suspected at fibular head use a stimulation site of 12-18 cm more proximal to the fibular head.

Anomalous innervation to the extensor digitorum brevis occurs in 1/5 patients (at least partially). Identified by inability to evoke a muscle action potential when stimulating at anterior ankle or a different shape (smaller) potential when stimulating here. This accessory nerve causes posterior to lateral malleolus so cathode should be placed here.

NORMAL VALUES

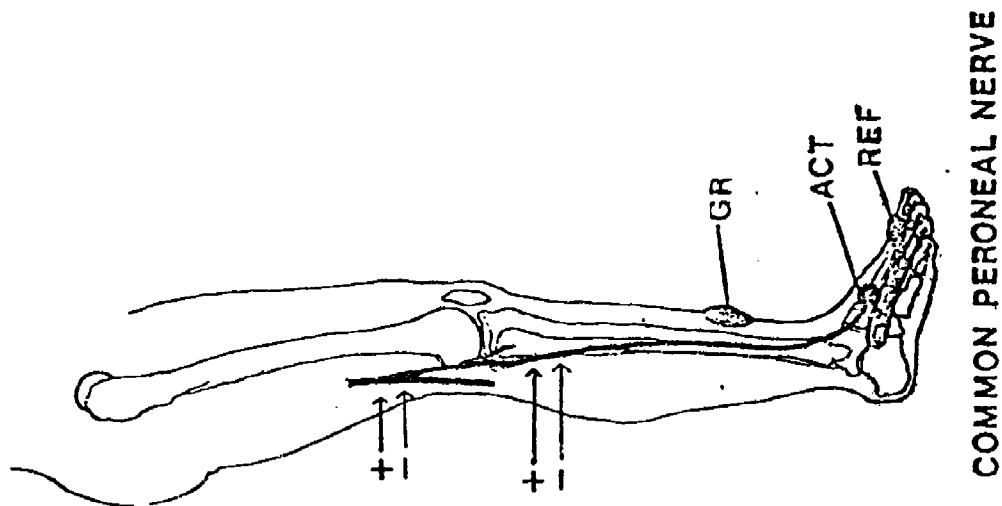
49.9 ± 5.9 M/sec

Distal latency: $4.5 \pm .8$ ms

Proximal latencies have been determined for use in below the knee amputees, and neuromuscular diseases where extensor digitorum brevis action potential cannot be elicited. Active electrode is placed 1/2 way down leg over middle of dorsiflexor muscle group and stimulation at fibular head.

NORMAL VALUES

5.5 - 7.2 ms (N = 217)

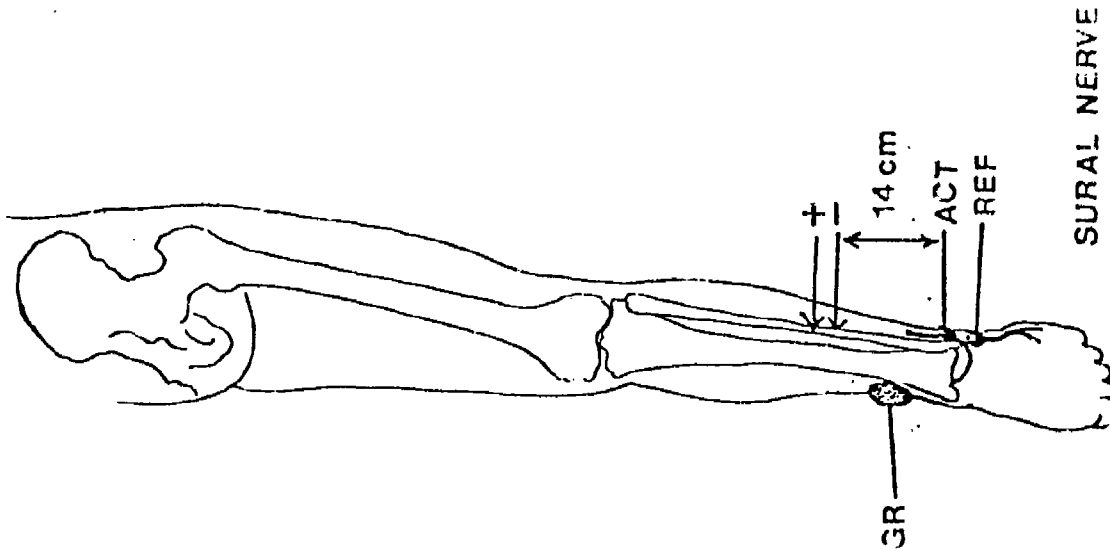


SURAL NERVE

(2) Active and recording electrodes are placed under lateral malleolus on lateral aspect of ankle. Sural nerve is stimulated as it pierces the gastrocnemius fascia just lateral to the midline of posterior distal calf, 10-18 cm proximal to active electrode. If leg is cold - a clue is prolonged latency of peroneal nerve - determine temperature. Subtract .1 ms (latency of activation) from the observed latency and divide into the distance.

NORMAL VALUES (after LaFratta)

<u>Age</u>	<u>(To Peak)</u>
20-29	44 ± 2.5 M/sec
30-39	38.80 ± 3.3 M/sec
40-49	36.70 ± 3.7 M/sec
50-59	37.20 ± 3.0 M/sec
60 & over	35.00 ± 3.8 M/sec



ULNAR NERVE

MOTOR CONDUCTION

- (3) Active electrode is placed over center of abductor digiti quinti; reference over proximal phalanx fifth digit. Stimulation (cathode) just radial to tendon of flexor carpi ulnaris 8 cm proximal to active electrode. Proximal site of stimulation should be just below ulnar groove and 18 cm proximal to ulnar groove on medial aspect of humerus.

N.B.: Elbow should be flexed to 70 degrees during procedure of stimulation and measurement to make more precise the actual length of ulnar nerve. More proximal stimulation sites include supraclavicular and C-8 root (see median nerve).

SENSORY CONDUCTION

Antidromic - ring electrodes over fifth digit separated by 4 cm. N.B. motor artifact may be interfering. Stimulate 14 cm proximal to active electrode at same site as motor stimulation.

Orthodromic - reverse stimulation and recording electrodes. More proximal sites of stimulation may also be done.

NORMAL VALUES

57 $\pm$ 4.7 M/sec - motor forearm segment
62.7 $\pm$ 5.5 M/sec - motor across elbow segment
56.7 $\pm$ 4.2 M/sec - sensory orthodromic (to peak)
54.9 $\pm$ 3.9 M/sec - sensory antidromic (to peak)

Distal Latency:

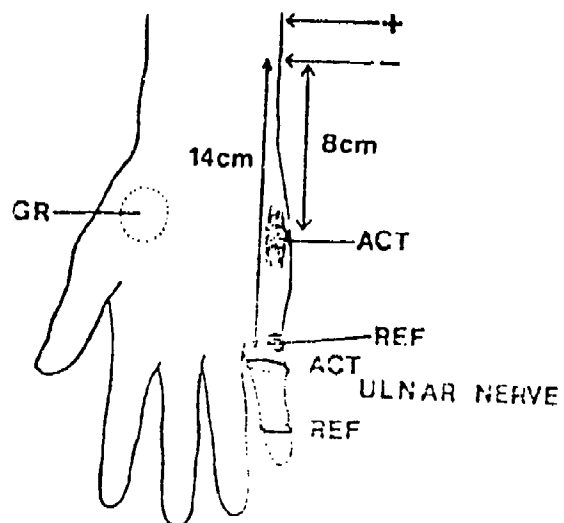
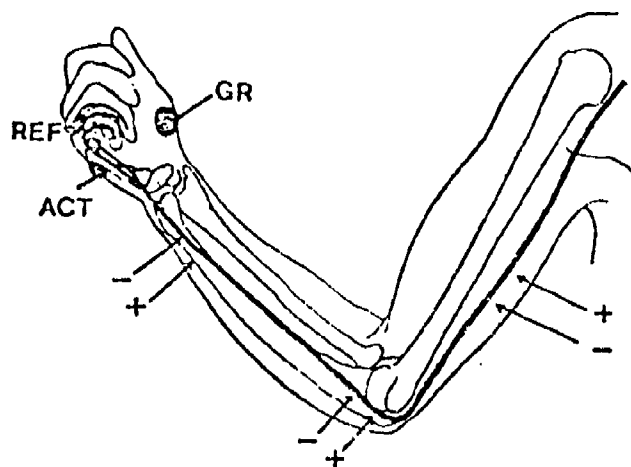
Motor: 3.7 $\pm$.3
Sensory: 3.0 $\pm$.25 Antidromic (peak)
3.0 $\pm$.25 Orthodromic (peak)

Muscle AP 8-20 mV

Sensory AP 15-50 mV

ADDENDUM

For deep branch surface recording electrode should be over adductor pollicis (i.e. just medial to thenar eminence on palmar surface of web space). Additional latency is .5 ms.



(e) Disposition

Forward the recorded results on the form attached to the examination package to the diagnostician.

(2) Psychological Battery

(a) General

(1) This battery yields objective numerical data, and is well-standardized and clinically validated. The individual tests were chosen to insure an adequate analysis of one of the major alleged manifestations of herbicide toxicity. Each test either validates one of the other tests, or is considered to be a "definitive" test for analysis of a suspected psycho/neuropathic effect.

(2) Compared to the general civilian population, characteristic response tendencies are observed on the MMPI and Cornell Index among active duty aircrewmembers being evaluated in an aeromedical setting. It is also important to consider the effect that pending retirement has exerted on the reporting of medical history and symptomatology. This may also alter responses to psychological testing.

(3) The battery requires approximately 5-1/2 to 6-3/4 hours to administer, depending on the speed of the examinee. An additional 1 to 2 hours of scoring and other clerical tasks will be required. Since test debriefing to clarify unusual performances, response biases, etc., is a crucial part of the psychologic evaluation, it is recommended that testing begin and be completed as early as possible during each examinee's stay at his respective evaluative facility.

(b) Specific Tests

(1) Wechsler Adult Intelligence Scale (WAIS): 60-75 minute individually-administered collection of verbal and nonverbal intellectual measures; also useful for clinical inferences when combined with the neuropsychological battery below.

(2) Reading subtest of the Wide Range Achievement Test (WRAT): 10-minute individually-administered measure of word recognition ability. Important to rule-out reading inefficiency should response to personality instruments below be of questionable validity (e.g., high F Scale on MMPI).

(3) Halstead-Reitan Neuropsychological Test Battery: 150-180 minute individually-administered collection of brain behavior relationship measures for establishing the functional integrity of the cerebral hemispheres. The battery must include the following subtests: Category, Tactual performance, Speech-Sounds, Seashore Rhythm, Finger Tapping, Trail

Making, and Grip Strengths. The Aphasia Screening and Sensory-Perceptual Exams are considered optional in view of their redundancy with the clinical neurologic exam included in this project. Individualized test debriefing is conducted to clarify test performances in the WAIS and Neuropsychological Battery.

(4) Three subtests of the Wechsler Memory Scale I (WMS I): 30-minute individually-administered measures of immediate and delayed recall of verbal and visual materials. The Logical Memory, Associate Learning and Visual Reproduction subtests are to be administered in the standard, immediate-recall fashion initially. After 30 minutes has elapsed, the examinee is asked, without prior alerting, to recall as much as he can about the Logical Memory and Visual Reproduction subtest stimuli. Standard scoring is used for both test-retest administrations.

(5) Cornell Index (CI): 10-15 minute selfadministered and standardized neuropsychiatric symptom and complaint inventory, including items involving asthenia, depression, anxiety, fatigue, and GI symptoms in lay language. Endorsement of items are to be explored and clarified in test-debriefing.

(6) Minnesota Multiphasic Personality Inventory (MMPI): 60 to 90 minute self administered clinical psychiatric screening instrument; also capable of estimating response biases (e.g., "fake good," or "fake bad"). The shortened version of Form R (i.e., items 1 to 399) may be substituted for the 566-item Long Form. Standard scoring and Minnesota norms are to be used, with the possible exception of active duty examinees where USAFSAM aircrew norms may be applied. Clarification of profiles showing response biases, questionable validity, and/or unusual item endorsements will be conducted in individual test debriefing.

(c) Examination Results

Forward all test materials as scored with annotations, interpretations, and impressions to the diagnostician for inclusion in the subject's examination file.

(d) Psychometrics: Special Instructions

(1) For the Cornell Index and MMPI, each subject is instructed: (a) to answer carefully every item; and (b) that wherever applicable, his responses should reflect personal experiences, beliefs, preferences, etc., only for the time period between his combat tour in SEA and the date of testing. These instruments are not to be group administered and a reasonable amount of privacy should be provided. These instruments should not be completed at the subject's overnight quarters nor anywhere else outside the supervised confines of the evaluative facility.

(2) If a subject's measured word recognition falls below the 6.5 Grade Level (Raw Score=40, Level II) according to the WRAT Reading subtest, the Cornell Index and MMPI are read aloud or administered via tape recording. In such cases, the subject retains the right to mark his answer sheet outside the view of the examiner or of others within hearing distance.

(3) All eleven subtests of the WAIS are administered, i.e., pro-rating of subtests is not allowed. The scoring of WAIS subtest items, and the operations of summing, transferring, and finding Raw Scores, Scaled Scores, and Tabled IQ values are double-checked for accuracy by the Psychologist in charge (or his/her appointed representative) before the raw data are forwarded to the diagnostician.

(4) Precautions similar to those in #3 above are exercised in the scoring and other clerical tasks associated with the Halstead-Reitan, WMS I, WRAT, Cornell, and MMPI.

(5) For the Halstead-Reitan, use as the preferred, or dominant, hand the one which the subject uses most in writing. If in doubt, administer a "Name Writing Test", where the subject is simply asked to write his name in a normal manner as though signing a personal check. The examiner measures the time for each hand to perform, (without alerting the subject to the timing), and assigns dominance to the quickest hand.

(6) For the grip strength measure, report the average, in kilograms, of 3 brief, but maximum, squeezes of the dynamometer for the preferred and the non-preferred hands. Alternate hands between trials.

(7) The Psychologist in charge will conduct a one-to-one test debriefing with each subject to estimate the test-by-test and overall accuracy and validity of the test results. A prepared form is provided for this purpose, and should be filled out completely before forwarding, with the subject's raw data, to the diagnostician. If applicable, input from the testing technician utilized is encouraged.

(3) Electrocardiogram

(a) A standard 12-lead scalar electrogram is required. If an arrhythmia is observed, a one minute rhythm strip is requested, in addition. The electrogram will be done following a minimum fast of four hours.

(b) Mounting: Mount the tracing in the usual manner of the laboratory for the recorder used.

(c) Disposition: Forward the mounted tracing and rhythm strip, if obtained, to the diagnostician.

(d) Interpretation:

The electrocardiograms will be interpreted by cardiologists at the examination center, and forwarded to USAFSAM/NG where physicians in the USAF Central ECG Library will compare the tracing to previous individual ECG records in the case of rated (pilot or navigator) subjects.

(e) Disposition (USAF Central ECG Library):

(1) Pilots and Navigators - The original tracings will be microfished and added to the individual's permanent record.

(2) Enlisted Subjects - The original tracings will be microfished and a permanent record established for each individual.

(4) Radiographic Examination

(a) Examination

A standard 14x17 in., standing, roentgenogram in the PA position using small nipple markers will be accomplished.

(b) Interpretation

A board-certified radiologist at the examination center will interpret the roentgenogram and record the results and forward them to the diagnostician.

(5) Pulmonary Function Studies

Standard evaluation of vital capacity and forced expiratory volume at 1 second will be performed.

(6) Laboratory Procedures

(a) General Instructions; First Day

(1) The patient should report in the morning in a fasting state having had water only after midnight. The patient will have been requested to eat approximately 150 gms of carbohydrate each of the three preceding days and to consume no alcoholic beverages. Non-compliance is not a contraindication to drawing the blood specimens. However, a notation of extent of noncompliance should be made by the examining physician to aid in the interpretation of the results.

(b) General Instructions; Second Day

Serum hormone levels should be determined from specimens collected on the morning of the second day. Hormonal levels appear to oscillate rapidly in a random fashion. Distributions drift with time suggesting

diurnal variations and some are affected by nonfasting state. Therefore, patients should be fasting prior to drawing blood for hormone analysis.

(c) Specific Tests to be Performed on all Participants

- (1) Hematocrit
- (2) Hemoglobin
- (3) RBC Indices
- (4) White Blood Cell Count and Differential
- (5) Platelet Count
- (6) Erythrocyte Sedimentation Rate
- (7) Urinalysis
- (8) Semen Analysis (Number, % Abnormal, Volume)
- (9) Blood Urea Nitrogen
- (10) Fasting Plasma Glucose
- (11) Creatinine
- (12) 2-hour Post Prandial Plasma Glucose
- (13) Differential Cortisol (0730 and 0930 hours)
- (14) Cholesterol & HDL
- (15) Triglycerides
- (16) Bilirubin, Total and Direct
- (17) SGOT
- (18) SGPT
- (19) GGTP
- (20) Alkaline Phosphatase
- (21) LDH
- (22) Serum Protein Electrophoresis
- (23) CPK

- (24) VDRL
- (25) LH
- (26) FSH
- (27) Testosterone
- (28) Thyroid Profile (RIA) (T₃, T₄, TSH,FTI)
- (29) Delta-aminolevulinic Acid
- (30) Urine Porphyrins
- (31) Hepatitis B antigen/antibodies (HB_sAg, anti HB_cAg, anti HB_sAg)
- (32) Prothrombin time
- (33) Blood Alcohol

(d) Tests to be performed on selected subjects

- (1) Anti-nuclear Antibody on subjects with evidence of autoimmune disorders
- (2) Hepatitis A Antigens/antibodies for those with current or past liver disease
- (3) Karyotyping for those fathering children with birth defects
- (4) Skin photography and skin biopsy on subjects with suspected chloracne
- (5) For those whose medical history indicates an increase in infectious diseases
 - (a) Immuno-electrophoresis
 - (b) Quantitative Immunoglobulin Determinations
- (6) To be performed on a randomly selected group of study subjects
 - (a) Enumeration of B and T cells
 - (b) Enumeration of Monocytes
 - (c) B and T cell function tests

(e) 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 squamocellular carcinomas of the lung were found.

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

(a) Skin: Chloracne, hirsutism.

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

(c) Renal: Hemorrhagic cystitis, focal Pyelonephritis.

(d) Neuromuscular System: Asthenia, i.e., headache, apathy, fatigue, anorexia, weight loss, sleep disturbances, decreased learning ability, decreased memory, dyspepsia, sweating, muscle pain, joint pain and sexual dysfunction.

(e) Endocrine System: Hypothyroidism.

(3) Based upon 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) Differential
 - (c) Serum protein electrophoresis
 - (d) Selective use of immunoelectrophoresis and quantitative immunoglobulin determination
 - (e) B cell and T cell counts and functions
- (6) Hepatic screen:
 - (a) SGOT
 - (b) SGPT
 - (c) GGTP
 - (d) Bilirubin, Total and Direct
 - (e) Alkaline phosphatase
 - (f) LDH
 - (g) Cholesterol

- (h) HDL
- (i) Triglyceride
- (j) Urine porphyrins
- (k) Urine porphobilinogen
- (l) Hepatitis B antigens/antibodies (HB_sAg, anti HB_cAg, anti HB_sAg)
- (7) Renal screen:
 - (a) Urinalysis
 - (b) BUN
 - (c) Creatinine
- (8) Endocrine screen
 - (a) Differential cortisol (0730 and 0930 hours)
 - (b) Thyroid profile (RIA)
 - (c) Fasting plasma glucose
- (9) Neuromuscular system: CPK
- (10) Elucidation of symptoms of asthenia:
 - (a) Testosterone
 - (b) LH
 - (c) FSH
- (11) The following tests should be performed only as follow-up for abnormalities in the history or physical examination findings:
 - (a) HAVAB (IgG and IgM)
 - (b) ANA

E. Forms

Anatomical Figure (Anterior)

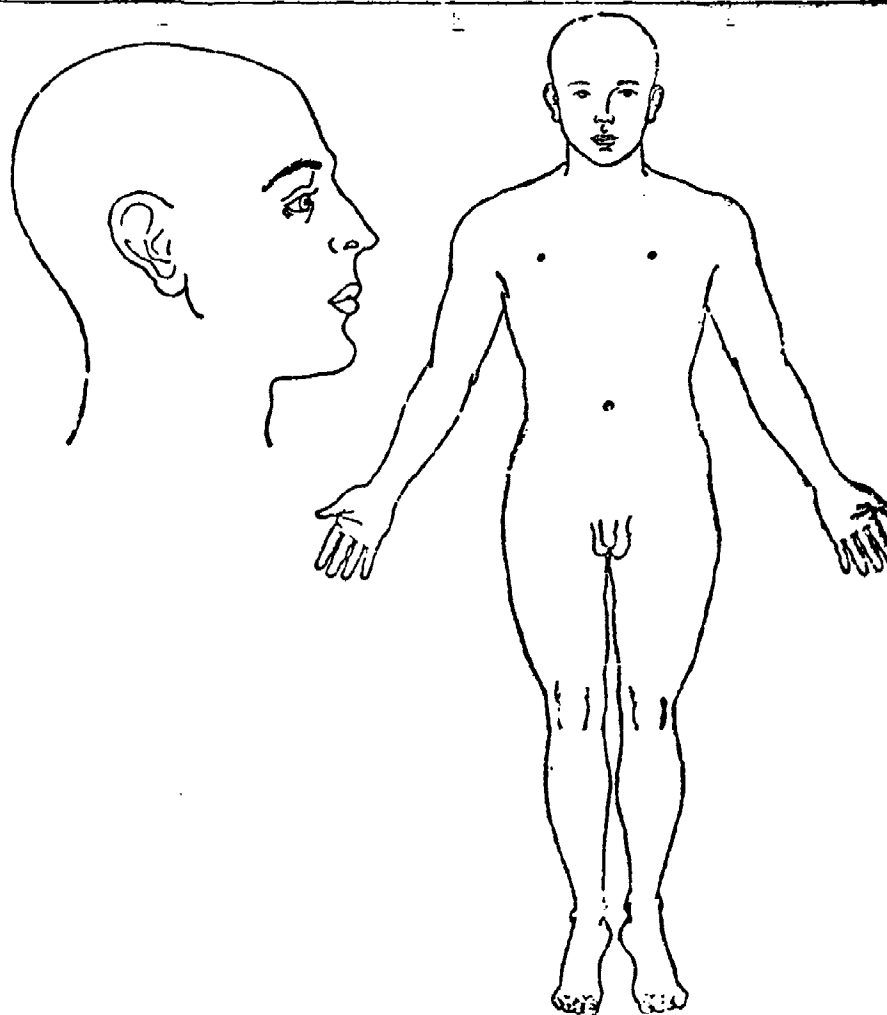
Anatomical Figure (Posterior)

Nerve Conduction Velocities

Psychometric De-Briefing Form

CLINICAL RECORD

ANATOMICAL FIGURE

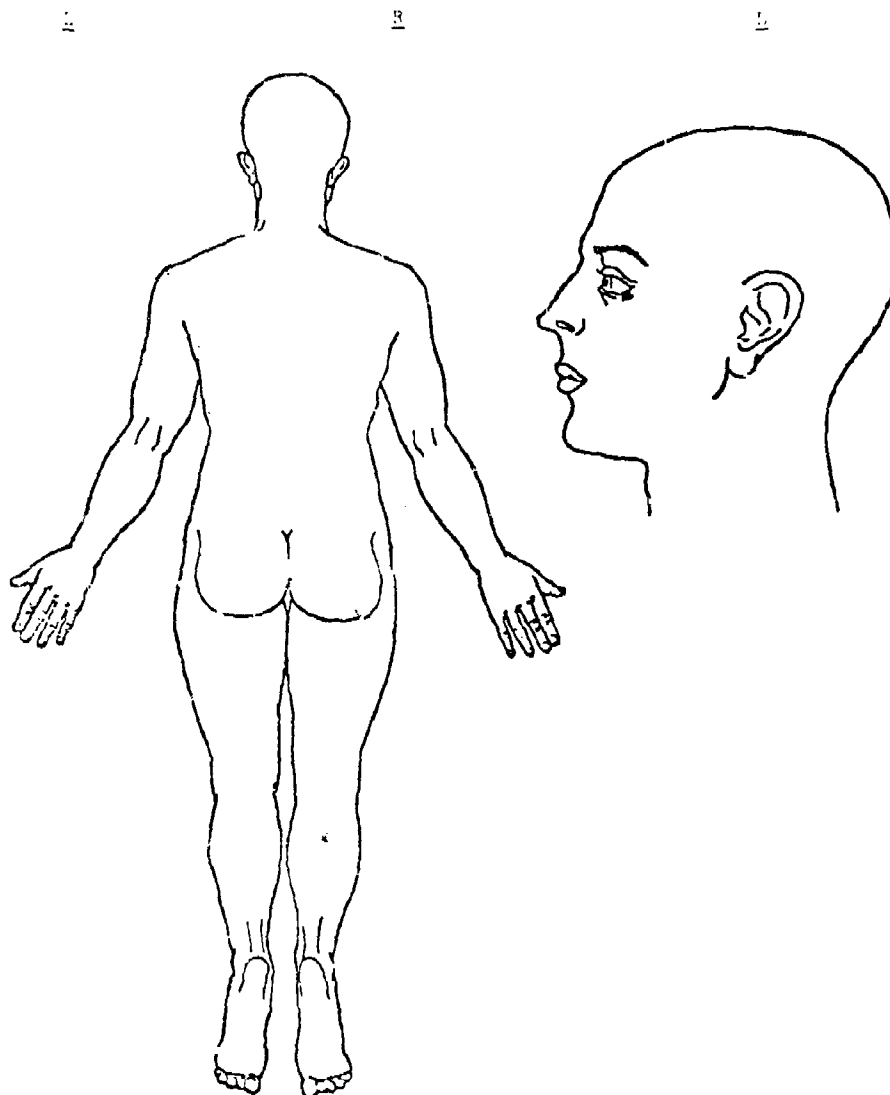


PATIENT IDENTIFICATION (For report or written entry give Name—last, first, middle, 2 sds, date, hospital or medical facility)

REGISTER NO.

WARTING

ANATOMICAL FIGURE
 Standard Form 687
 16-136



U.S. GOVERNMENT PRINTING OFFICE: 1967

PAGE NO.		NERVE CONDUCTION VELOCITIES			
SOCIAL SECURITY NUMBER		NAME (Last, First, MI)		GRADE	CASE NO.
DATE OF EXAMINATION		AGE			
YEAR	MONTH	DAY			
			DATE: _____ TIME: _____ TEMP: _____		

1. Ulnar (one side only) ☐ R ☐ L Elbow ☐ Above ☐ Below

Normal Values for Laboratory

Latency / / / / ms / / / /

Distance / / / / mm / / / /

N.C.V. / / / / m/s / / / /

Stm. Curr. / / / / mV / / / /

2. Peroneal (one side only) ☐ R ☐ L

Normal Values for Laboratory

Latency / / / / ms / / / /

Distance / / / / mm / / / /

N.C.V. / / / / m/s / / / /

Stm. Curr. / / / / mV / / / /

3. Sural (one side only) ☐ R ☐ L (If unobtainable, Median or Ulnar Sensory recommend)

Normal Values for Laboratory

Latency / / / / ms / / / /

Distance / / / / mm / / / /

N.C.V. / / / / m/s / / / /

Stm. Curr. / / / / mV / / / /

Ranch Hand II: Psychometric De-Briefing Form

Subject: _____

Name	Test Date	Eval Facility	R L
			Handedness

Psychologist/ De-Briefer :						Yes	No
	<u>Name</u>	<u>Title</u>	<u>Degree</u>	<u>Clin/Couns</u>		<u>Cert/Lic</u>	

<u>Testing Technician:</u>	<u>Same as above</u>	<u>Name</u>	<u>Degree</u>	<u>Test/Experience (Yrs)</u>
----------------------------	----------------------	-------------	---------------	------------------------------

Instructions

In the appropriate column below, indicate the test-by-test validity of the psychometric results based upon the Examiner's observations of the subject during testing and upon the Psychologist's evaluation of the data in test debriefing with the subject. Use the numbered factors below to indicate the reason(s) for questionable validity among any of the data. For datum thought to be of questionable validity, also provide an estimate of the subject's "true" score or result. Forward the completed form with the subject's raw data.

Reasons for Questionable Validity

1. Poor reading comprehension
2. Fatigue
3. Neg attitude, angry, marginal cooperator
4. Careless, hurried responses
5. Examiner Error
6. Exaggeration of complaints ("fake bad")
7. Minimizing complaints ("fake good")
8. Disorganized personality (Psychotic)
9. Physically ill (flu, venipuncture effects, etc)
10. Other (Specify _____)

<u>Test Score</u>	<u>Valid Results</u>	<u>Reason(s) for Questionably Valid Results</u>	<u>Est of "True" Score/Result</u>
1. WAIS VIQ PIQ FSIQ			
2. WRAT Reading			
3. Halstead-Reitan Category Test			

Ranch Hand II: Psychometric De-Briefing Form Continued

<u>Test Score</u>	<u>Valid Results</u>	<u>Reason(s) for Questionably Valid Results</u>	<u>Est of "True" Score/Result</u>
Tactual Performance Test			
Preferred Hand			
Non-Preferred Hand			
Both Hands			
Memory			
Localization			
Speech-Sounds Perception			
Seashore Rhythm			
Finger Tapping			
Preferred Hand			
Non-Preferred Hand			
Trail Making Test			
Part A			
Part B			
Grip Strengths			
Preferred Hand			
Non-Preferred Hand			
4. WMS I			
Logical Mem (immed)			
Visual Repro (immed)			
Associate Lrng			
Logical Mem (delayed)			
Visual Repro (delayed)			
5. Cornell Index			
6. MMPI (overall rating of protocol)			WNL or ONL

XVII. ANNEX 1 - EXPOSURE INDEX CONSTRUCTION

When exposure concepts were initially discussed, the principal investigators were optimistic about the feasibility of developing an exposure estimate or index which was specific to the individual study subject. However, as the investigators became more familiar with the operational environment of the Vietnam War and the limitations of the personnel records system, it became obvious that a validated individual-specific exposure index could not be developed. This specific index was dependent on the availability of operational records containing individual flying time data and aircraft maintenance records containing the names of ground support crew members. Because this data was unobtainable, a less specific exposure concept was then developed. This index was to be base-specific rather than individual-specific, and is the index presented in the protocol in this technical report. However, further inquiry disappointingly showed once again that available data sources would not provide adequate information to support the construction of this index. The base-specific index relied upon records to provide a quantitative measurement of the number of missions and amount and type of herbicides sprayed by air crews from each base. This index assumed that all personnel at a given base shared equally in the workload. Unfortunately, the "Herbs tapes" did not specify the base to which spray aircraft were assigned, and the military personnel records did not definitively specify the exact duty locations of all personnel. Thus, a still more generalized exposure concept was necessary.

Although the more refined indices could not be validly applied, it was feasible to develop an exposure index for this study which can be validated, fulfills the requirements of the study design, and is fully supported by available data sources. A crude index can be developed and applied universally to all exposed subjects, regardless of their assigned duties in Vietnam. This index is based solely on the amount of dioxin disseminated throughout Vietnam each month from January 1962 through April 1970. The data to support this index are based on a comprehensive listing of herbicide missions, being developed by the Department of Defense, and estimates of the TCDD content of 2,4,5-T over time. These estimates are being developed and refined at USAFSAM at the present time. A refined exposure index for ground crew members is also feasible and is under development. This index builds on the crude index and takes the experience of ground crew members into account. It also assumes that each individual assigned to these duties in the Vietnam theater carried out his share of the workload in his specialty. This "experience factor" is constructed by dividing the total number of herbicide spray sorties flown during a subject's tour of duty by the number of individuals performing the subject's duties during the period of his tour. Similarly, a refined air crew index can be constructed. This index expands the concept of the ground crew index by including a factor reflecting the variable levels of exposure within the C-123 aircraft. Simulant studies to quantify these differences were conducted, and plans are underway to repeat these studies to revalidate the conclusions.

Symbolic representations of these indices are shown below:

Crude Exposure Index:

$$E_1 = \left\{ \begin{array}{l} \text{TCDD sprayed in the} \\ \text{Vietnam Theater during} \\ \text{the 1th subject's tour} \end{array} \right\}$$

Refined Ground Crew Exposure Index:

$$E_{1}^{\text{GND}} = \left\{ \begin{array}{l} \text{TCDD sprayed in} \\ \text{the Vietnam} \\ \text{theater during} \\ \text{the 1th subject's} \\ \text{tour} \end{array} \right\} \times \left\{ \begin{array}{l} \text{Herbicide sorties} \\ \text{performed in the Vietnam} \\ \text{theater during the 1th} \\ \text{subject's tour} \\ \hline \text{Number of ground crew} \\ \text{personnel (job specified)} \\ \text{in the Vietnam theater} \\ \text{during the 1th subject's} \\ \text{tour} \end{array} \right\}$$

Refined Air Crew Exposure Index:

$$E_{1}^{\text{AIR}} = \left\{ \begin{array}{l} \text{TCDD sprayed in} \\ \text{the Vietnam} \\ \text{theater during} \\ \text{the 1th subject's} \\ \text{tour} \end{array} \right\} \times \left\{ \begin{array}{l} \text{Herbicide sorties performed} \\ \text{in the Vietnam theater} \\ \text{during the 1th subject's} \\ \text{tour} \\ \hline \text{Number of airmen with} \\ \text{subject's duties in the} \\ \text{Vietnam theater during the} \\ \text{1th subject's tour} \end{array} \right\}$$

$$\times \left\{ \begin{array}{l} \text{Crew position} \\ \text{weight of the} \\ \text{1th subject} \end{array} \right\}$$

(total amount) X (experience) X (intensity)

The data required to support these indices are either currently available or are in the final stages of development. These indices are feasible and will adequately support the analytic strategy of the study design.

XVIII. ANNEX 2 - COMPARISON GROUP INELIGIBILITY

A central element of epidemiologic research is study population ascertainment. Incomplete population ascertainment always carries with it the possibility of serious selection bias which cannot be corrected using statistical procedures. Complete ascertainment of the exposed and comparison populations occurred through a manual review of military personnel records from 1962-1964, combined with a computer tape generated by the Air Force Human Resources Laboratory (AFHRL). This computer tape was based on retrieval parameters identified to AFHRL by the United States Air Force School of Aerospace Medicine (USAFSAM) principal investigators. The retrieval process required computer searches of multiple Air Force Military Personnel Center tapes spanning the time period of January 1965 through December 1971. In November of 1980, AFHRL delivered to USAFSAM a tape that was thought to contain the total eligible study population. The study match was completed and the selected individuals were contacted to participate in the study. In December of 1981, Louis Harris and Associates, the questionnaire administration contractor, notified the USAFSAM investigators that several of the participants had reported no experience in Southeast Asia, suggesting that there had been overselection. Review of these participants' military personnel records clearly revealed that they were comparison subjects who had not had Southeast Asia experience. In order to maintain the integrity of the questionnaire implementation and the physical examination contract, it was necessary to implement a modification of the replacement strategy which had been originally designed for use with control subjects who refused to participate in the study. It had been intended that the noncompliance questionnaire be given to both the replacement and the refusing subjects, and that they would be matched for equivalent health perception prior to implementing this strategy. However, the early requirement to replace these ineligible individuals did not allow the use of the noncompliant instrument. The eligibility of replacement candidates was verified and these valid subjects were entered into the study. Inappropriate subjects were informed of this selection error and excluded from further participation in the effort. Two hundred eleven inappropriate subjects had been interviewed, and 26 had been examined.

This situation also necessitated an immediate manual review of the personnel records of all individuals for the comparison group. The review of records was completed in March of 1982 and the verification of this process was initiated. The objective of this quality control effort was to verify the eligibility of the comparison group by subsampling techniques and to insure that errors in excess of one percent ineligibility did not exist. The estimated error rate was found to be 0.00748% with confidence bounds of 0.00340% and 0.0312%. To further reduce this error rate, each replacement candidate's personnel records were re-evaluated prior to forwarding his name to the questionnaire contractor, thereby assuring that all replacements were absolutely eligible for the study. The overall review demonstrated that 18% of the 12,193 individuals in the original control population were erroneously included. These ineligible subjects were randomly distributed throughout the C1-C10 matrix. Two percent of this error was due to inaccurate data on the USAF personnel tape and 16% due to incorrect cohort selection specification and/or computer search implementation. All errors were in the direction of overselection, due to the inclusion of non-Southeast Asia C-130 units in the specifications.

Following the removal of the ineligible subjects from the cohort matrix, the empty positions were then filled by valid comparison subjects with higher cohort numbers, thus constituting a leftward shift of the matrix. This process was reviewed by the subcommittee of the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants and members of one of the other peer review groups prior to implementation, and its use was found to be totally acceptable. Its use resulted in a reduction of the study from 1:10 to a 1:8 design. Monte Carlo studies using current physical examination compliance rates showed this collapse to have not significant impact on statistical power in the followup phase of the study. Although the shift-left process constituted an unplanned use of the replacement strategy, it permitted the continuation of both the questionnaire and physical examination contracts without disruption and with total validity.

XIX. ANNEX 3 - SUPPLEMENTAL ANALYSES

The study is of distinct benefit to the herbicide-exposed group since it may provide the individuals with an early warning of herbicide effects if they are occurring; or if no herbicide effects are uncovered, the study can provide some peace of mind by contributing to settlement of the public controversy. The study, however, is also of very significant benefit to unexposed individuals participating in the effort as comparison subjects. These additional returns occur because of the nature of the study design and the analytic flexibility inherent in that design.

Except for the skin condition called chloracne, none of the disease entities that have been related to herbicide exposure are unique to that exposure. Processes such as peripheral neuropathy, teratogenesis, and carcinogenesis have been reported in laboratory studies with animals or in epidemiologic studies of herbicide; but these processes also occur somewhat commonly in general populations without herbicide exposure. Thus, to determine the occurrence of a true herbicide effect, this epidemiologic study is gathering data on other factors known or suspected to produce disease, and which could obscure herbicide effects. Among these potentially confounding factors are several military and civilian occupational exposures to chemical, physical, and biologic agents including: asbestos, x-ray or nuclear radiation, industrial chemicals, insecticides or pesticides, and prior infectious disease processes. By studying possible correlations between these factors and disease processes, benefits accrue to both the herbicide-exposed and unexposed subjects. Correlations between disease incidences and other potentially causative factors will be sought using statistical data-processing techniques such as multivariate regression or analysis of variance. This approach will identify herbicide effects in a fair and equitable manner as described in the protocol, but it will also provide additional medical data of significant direct interest in its own right.

Glossary of Abbreviations

<u>ABBREVIATION</u>	<u>DEFINITION</u>
AFSC	Air Force Specialty Code
ALK PHOS	Alkaline Phosphatase
AMD	Aerospace Medical Division, Brooks AFB, Texas - supervises all medical research activities within the Air Force Systems Command
AV-GAS	Leaded Aviation Fuel (Reciprocating Engine)
BUN	Blood Urea Nitrogen
C-7	USAF Cargo Aircraft, 2 engine, Propeller, Reciprocating
C-123	USAF Cargo Aircraft, 2 engine, Propeller, Reciprocating
C-130	USAF Cargo Aircraft, 4 engines, Turbo-Propeller
CBC	Complete Blood Count
CPK	Creatine Phosphokinase
CSF	Cerebrospinal Fluid
Det 1 AMD	Onsite physical examination contract monitor
DNA	Deoxyribonucleic acid
DOD	Department of Defense
2,4-D	2,4-dichlorophenoxyacetic acid
ECG	Electrocardiogram
EPA	Environmental Protection Agency
FBS	Fasting Blood Sugar
FSH	Follicle Stimulating Hormone
G.I.	Gastrointestinal
GAO	General Accounting Office
GGTP	Glutaryl-glutamic Transpeptidase
HDL	High Density Lipid
Herbicide Orange	Mixture of 2,4-D and 2,4,5-T contaminated with TCDD
Herbicide Pink Purple Green	} Other 2,4,5-T/TCDD-containing herbicides
JP-4	
LDH	Jet Fuel
LD50	Lactose Dehydrogenase
LH	(Median) Lethal Dose for 50% of Tested Animals
NCI	Luteinizing Hormone
MMPI	National Cancer Institute
PACER HO	Minnesota Multiphasic Personality Inventory
PACER IV	Code Name for the Herbicide Incineration Project
RANCH HAND	Code Name for the Movement and Storage of Herbicides at Johnston Island
	USAF Organizational Code Name for the Defoliation Operations in Vietnam

ABBREVIATIONDEFINITION

RBC	Red Blood Cell
RIA	Radio-immuno Assay
RVN	Republic of Vietnam
SEA	Southeast Asia
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMR	Standardized Mortality Ratio
SSS	Sensation Seeking Scale
SYSTO	Systems Officer
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TDY	Temporary Duty
TLV	Threshold Limit Value
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
USAF	United States Air Force
USAFSAM	United States Air Force School of Aerospace Medicine
USSR	Union of Soviet Socialist Republics
VA	Veterans Administration
VDRL/FTA	Serological Tests for Syphilis
WAIS	Wechsler Adult Intelligence Scale
WRAT	Wide Range Achievement Test