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FILE: RANCH HAND II

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PROTOCOL

PROJECT RANCH HAND II

EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO "HERBICIDE ORANGE"

MATCHED COHORT DESIGN

PREPARED BY: EPIDEMIOLOGY DIVISION
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USAF SCHOOL OF AEROSPACE
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Glossary of Abbreviations

ABBREVIATION	DEFINITION
AFSC	Air Force Specialty Code
ALK PHOS	Alkaline Phosphatase
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, Propeller/Jet
CBC	Complete Blood Count
CPK	Creatine Phosphokinase
CSF	Cerebrospinal Fluid
DNA	Deoxyribonucleic acid
DOD	Department of Defense
2,4-D	2,4 - dichlorophenoxyacetic acid
ECG	Electrocardiogram
EPA	Environmental Protection Agency
FBS	Fasting Blood Suger
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 containing herbicides
JP-4	Jet Fuel
LDH	Lactose Dehydrogenase
LD_{50}	(Median) Lethal Dose for 50% of Tested Animals
LH	Luteinizing Hormone
NCI	National Cancer Institute
MMPI	Minnesota Multiphasic Personality Inventory
PACER HO	Code Name for the Herbicide Incineration Project
PACER IVY	Code Name for the Movement and Storage of Herbicides at Johnston Island
PMR	Proportionate Morality Ratio
RANCH HAND	USAF Organizational Code for the Defoliation Operations
RBC	Red Blood Cell
RIA	Radio-immuno Assay
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase

ABBREVIATION	DEFINITION
SMR	Standardized Mortality Ratio
SSS	Sensation Seeking Scale
TCDD	2,3,7,8 - tetrachlorodibenzo-p-dioxin
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

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PROJECT RANCH HAND II

Executive Summary of 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 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 1970 was terminated when it became know that a contaminant, TCDD, was present in 2,4,5-T containing herbicides and that this contaminant caused congenital abnormalities when administered to pregnant rodents. Subsequent extensive research into the toxicity of TCDD in animals remains equivocal. Presently, the potential for teratogenicity and carcinogenicity of TCDD is significant but appears to be 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, 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 epidemiological studies dealing with TCDD exposure in humans have suffered from weaknesses in design, statistical power and inferences. These studies have only validated a link between TCDD exposure and the subsequent development of chloracne. The public's perception of the toxicity of "Herbicide Orange"/TCDD is generally different than that of the scientific community. A review of 500 veteran claims submitted to the Veterans Administration supports this fact and reveals an awesome spectrum of alleged symptoms and diseases.

This study design incorporates a matched cohort design placed in a non-concurrent prospective setting (incorporating "retrospective", cross-sectional and prospective phases). The study will begin on 15 October 1979. Detailed computer searches of Air Force personnel records, with several cross verifying approaches, will ensure total ascertainment of the RANCH HAND population. A group of C-130 crewmembers and support personnel will form the control group. They will be tightly matched to Ranch Hand personnel for the variables of age, AFSC, length of time in Vietnam, and race. Since there was a documented higher concentration of TCDD contamination prior to 1965, this factor will be considered in estimating an exposure index. Approximately 1000 Ranch Hand personnel will be matched to 10,000 potential controls, with the "best-fit", C-130 match, serving as a primary control. In the analysis of mortality, each exposed subject and the three best matched controls will be followed yearly. The "best fit" (primary) control will be entered into the questionnaire and physical examination phases of the study. If a primary control drops out, the next best control will be selected (sampling without replacement) so that both statistical power and loss to study difficulties in the prospective phase may be improved. All RANCH HAND

personnel and their primary controls will be asked to complete a telephone questionnaire and will be offered a comprehensive physical examination, with special emphasis being placed on dermatologic, neuropsychiatric, hepatic, reproductive and neoplastic conditions. An adaptive physical examination and questionnaire will be developed to be used in the prospective phase, which is initially set for five years duration. The unusual capabilities of the USAF in the collection, storage, and retrieval of data will allow integration of the various data collection methods used throughout the study. Expected biases and study difficulties include differences in group accountability, risk taking behavior bias in the volunteer RANCH HAND group, response bias, interview bias, loss to study difficulties, and variability of procedures performed, as well as the political overlay of this effort.

Since this study is dealing with an unknown clinical endpoint, determination of a disease state 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 in the prospective phase. 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 determination of a disease state. Beyond these pair-wise and group comparisons, newer techniques of pattern recognition, such as Factor Analysis and Cluster Theory, are being considered in order to achieve a more automatic and objective analysis. Mortality data will be analyzed using several different approaches, including age and age-disease specific rates, proportionate mortality rates, modified life table approaches, as well as more sophisticated logistic and multiplicative models. Analysis of questionnaire and physical examination data will utilize long-linear models to verify the appropriateness of the standard statistical methodologies (e.g., McNemar's test for dichotomous rates). Polytomous or categorical findings will be analyzed by the use of long-linear models. Continuous variables will undergo covariance analysis to remove non-controlled effects, followed by the use of a paired difference "t" statistic. Some data will naturally fall into groups (e.g., fertility/reproduction, liver function tests) in which case, multi-way contingency table analysis or extensions of the generalized linear model analyses will be used.

Work is continuing on protocol refinements, on population refinements and ascetainment, tolerance limits for matchings, index statistics, exact power calculations, and software analytic formats.

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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 investigation is to determine, by epidemiologic techniques, whether long-term health effects exist and can be attributed to occupational exposure to "Herbicide Orange."

II. Synopsis of Background

A. Current

News media presentations have recently focused medical, political and lay attention on possible adverse health effects in military personnel, allegedly due to Herbicide Orange [a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic 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. This defoliant was later found to have been contaminated with the toxin 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Figure A-1, Section XII). Approximately 500 claims for compensation have been filed against the Veterans Administration (VA), largely by former US Army members. 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.

B. Use of Herbicides

Research and development on phenoxy herbicides began in the early 1940s. Most of the initial phytotoxic screening programs and 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 Department of Defense procured approximately 34 percent (53 million pounds) of the total US production for use in South Vietnam. However, 8.9 million pounds of that amount were not sprayed in South Vietnam, but rather 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 were received at Tan Son Nhut Air Base, Republic of Vietnam, on 9 January 1962. These compounds were 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%

(4) Herbicide Orange (used from early 1965 through 15 April 1970)

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

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

In addition, two other herbicides were widely used in South Vietnam. These were Herbicide Blue (an organic arsenical formulated the sodium salt of cacodylic acid), and Herbicide White)a water soluable triisopropanolamine salt formulation of 2,4-D and picloram). The amount of the various herbicides used in South Vietnam from January 1962 through April 1970 are shown in Table 1.

Table 1. Estimated Quantities of Herbicides and TCDD Sprayed in South Vietnam, Jan 1962-Feb 1971

CHEMICAL		POUNDS
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

Concurrent with the change to Herbicide Orange, the scope aerial use shifted from four rotating aircrews to 30 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 non-populated areas and in April 1970, all uses of the herbicide were halted. In February 1971, all remaining stocks of 2,4,5-T containing herbicides were removed from South Vietnam, and transported to Johnston Island, Pacific Ocean, for open storage (Project PACER

IVY), and incinerated 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

From the above background, three interdependent study goals emerge:

A. Health

(1) To identify veteran and active duty individuals with adverse health effects (physical and psychological) if any, which are attributed to herbicide exposure, and

(2) To identify other individuals at risk of developing future adverse health effects, if any.

B. Political

To satisfy the social concern for proper investigation voiced both by lay and scientific communities, both national and international.

C. Legal

To clarify the question of compensation awards to the 500 claimants.

With regard to the goal of legal clarification, it is apparent that data and conclusions arising from this investigation, positive, negative, or indeterminant, will probably be used to better assess the issue of long-term health effects and resultant compensation. The operational assumption of this study, therefore, is: Air Force Operation RANCH HAND personnel probably received a greater average occupational exposure to 2,4,5-T and TCDD than US Army ground personnel, implying that RANCH HAND personnel should develop greater numbers of acute and chronic clinical signs/symptoms from the exposure, and should manifest them sooner than US Army personnel, if indeed there are any adverse long-term health effects at all. This dose-response notion suggests that although the Air Force population is not the best one to study, it is probably better than the Army population.

The overall scientific thrust of this investigation is to define the natural history of disease, if any, and its spectrum of illness, by direct and indirect methodology.

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. Most early studies used a myriad of herbicide formulations and unknowingly dealt with physically and chemically impure compounds. 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 and repetitive clinical finding associated with acute exposure to 2,4,5-T herbicide has been chloracne, recognized by most workers as the herald sign of acute overexposure to the herbicide. It is now recognized that the chloracne was caused by the presence of TCDD rather than the 2,4,5-T. Sequaelae 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 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 factors.

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

(1) 2,4-D

The pharmocokinetics of 2,4-D have been well studied in animals. 2,4-D is readily absorbed on oral administration. Initially, it is 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 is approximately 3 to 12 hours, with 2,4-D primarily eliminated from the body by the kidney, the rate of elimination being dose-dependent. 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 in the various animals. These differences are supposedly due to variations in species, age, dose levels, route of administration and chemical formulation used in the various studies. The distribution is generally ubiquitous throughout the body with the exception of hamsters, which show no placental passage, and mice, which show placental passage but only in late gestation. Clearance from plasma and the body varies greatly among animals 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 its unmetabolized form. However, at higher doses or more chronic doses, elimination entails a more active role by the liver (i.e.,conjugation). Higher doses and repeated lower doses appear to result in accumulation in animal tissues.

(3) TCDD

The information on the absorption, distribution and excretion of TCDD has been mostly derived from animal models. The only reported human study dealing with pharmacokinetics of TCDD dealt with the analysis of TCDD in tissues at necropsy of one case of confirmed TCDD exposure subsequent to the accidental release of TCDD in Seveso, Italy in July 1976. Studies in rats, mice and guinea pigs generally show that intestinal absorption of TCDD is relatively complete, with a large proportion of TCDD remaining 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.

(4) 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. Rapid absorption

has been observed after oral administration of 2,4-D or 2,4,5-T. The main 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 phenoxy herbicides are unmetabolized prior to excretion. 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 a 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/m^3 for either 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 or 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 dedrumming operations involving Herbicide Orange were at least two orders of magnitude below the TLVs.

C. Proposed Cellular Mechanism of Action for TCDD

TCDD has, in general, 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 are implicated in the development of cutaneous porphyria. The induction of aryl hydrocarbon hydroxylase and other mixed-function oxygenases/oxidases have been associated with carcinogenesis and tumorogenesis. 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. In a similar fashion to the acridine family of compounds, TCDD, because of its planar ring structure, is felt to "intercalate" with DNA resulting in "frame-shift" mutations. A few laboratory studies with bacterial systems, e.g., Escherichia coli and Salmonella typhimurium, or in one plant system, e.g., the African Blood Lily, have identified TCDD as being able to produce chromosome 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.

The effect of some nonspecific activity or as of yet unspecified toxicity continues to serve as a 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. In addition, TCDD's concentration in the adipose tissue suggests the possibility that under situations of weight loss (e.g., life style, medical indications, or disease), TCDD may be released into the circulation. Such a 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., 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.

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. 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 the Appendix, Table A-1. It is apparent that the toxic effects of 2,4-D and 2,4,5-T are markedly different from 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 potential which appears 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 LD_{50} in the guinea pig is 1 μg/kg compared to 1000 μg/kg in the dog), excretion (2,4,5-T plasma half-life in rats is 4.7 hrs compared to 77 hrs in dog), and oncogenicity (TCDD is oncogenic in rats but not shown to be oncogenic in mice under similar conditions). 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 designing human studies.

A second area of interest noted in the literature is a possible dose-response paradox in nonhuman primates (rhesus monkey) following exposure to TCDD. Animals receiving subtoxic doses in single-dose acute toxicity studies (LD_{50} determinations) have not been followed over long periods of time. Animals on chronic exposure studies 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 the accumulated dose was approximately 1 μg/kg body weight. Therefore, it remains unclear whether the toxicity demonstrated in chronic exposure studies is dependent upon a low level daily exposure accumulated to 1 μg/kg or would also be demonstrated following a single dose of 1 μg/kg.

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. Most of the patients discussed in these reports were exposed to multiple chemical agents and, therefore, 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 to 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. Hepatic dysfunction, renal, gastrointestinal and cardiac disturbances are "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 asthenic syndrome, peripheral neuropathy and hepatic dysfunction are of particular interest. Other symptoms of systemic toxicity occur, but usually resolve within 4-6 weeks. The peripheral neuropathy associated 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 times. One autopsy study demonstrated a demyelination process within the brain of a 76-year-old male who committed suicide by ingestion of 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 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 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. Porphyria 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.

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 appear in current news media productions. A similar incident in Missouri in 1971 is

often cited. Six children and two adults experienced chloracne after accidental exposure to TCDD, but all were healthy after five years of followup study. A final prospective assessment of fertility, teratogenesis and carcinogenesis will probably be made in the future.

F. Veteran Complaints

The Veterans Administration Compensation and Pension Service, Washington, DC, provided data on 361 claims filed as of 30 April 1979, submitted by veterans alleging an altered health status due to exposure to Herbicide Orange. A review of these claims revealed that less than half of the veterans received detailed physical examinations to evaluate the claims. Numerous media presentations emphasizing both military and civilian herbicide exposures have alleged a remarkably wide spectrum of health effects being claimed by the veterans. Based on current guidelines established by the Veterans Administration (Program Guide 21-1, Section 0-18 and Title 38 USC), none of the symptoms cited in these claims were shown to be secondary to exposure to Herbicide Orange. The vast majority of the exposure claims remained unsubstantiated, based on review of military personnel and medical records. The guidelines state that the only chronic residual of defoliant exposure ever incriminated by clinical history has been chloracne. Furthermore, chloracne was associated with prolonged intensive exposure and all other toxic effects of the herbicide were viewed to be rapid in onset and to run a brief course followed by recovery without residual disease. In fact, the vast majority of the claims alleging exposure to Herbicide Orange were not for chloracne and, as a result, did not satisfy the criteria set forth for compensation. Of the three claims dealing specifically with chloracne, none were confirmed by physical examination.

Table 2 summarizes the descriptive characteristics of the 361 claimants, while Table 3 summarizes the distribution of symptom category complaints.

Table 2

SUMMARY OF DESCRIPTIVE CHARACTERISTICS OF HERBICIDE RELATED CLAIMS SUBMITTED TO THE VETERANS ADMINISTRATION AS OF 30 APRIL 1979*

Total Number of Claims: 361
Sex: 100% Male
Mean Age: 34 years
Mean Number of Alleged Symptoms per Veteran: 2.3
Branch of Service: (Service history identified in 66.8% of claims)

US Army	66.4%
US Marine Corp	17.4%
US Air Force	11.2%
US Navy	5.0%

*Exact racial distribution unknown; anecdotal information suggests the majority of claimants are non-Caucasian.

Table 3

HERBICIDE RELATED CLAIMS SUBMITTED TO THE VETERANS ADMINISTRATION BY SYMPTOM CATEGORY AS OF 30 APRIL 1979

Total Number of Claims: 361-13 = 348*

		PERCENT
DERMATOLOGIC	(hairloss; chloracne; tinea, eczema, contact dermatitis, keloid, vitiligo, tumors, porphyria)	48.9
PSYCHIATRIC	(personality disorders, anxiety neurosis, depression, psychoses, pedophilia, alcoholism, adjustment reactions)	27.6
EAR, NOSE, & THROAT	(hearing loss, tinnitus, voice loss, sinusitis)	14.4
CANCER	(lung, bone, pancreas, brain, thyroid, larynx, colon, skin, soft palate, leukemia, lymphomas, Hodgkins Disease)	13.8
PERIPHERAL NEUROPATHY	(numbness, paresthesia, weakness, tingling, Guillan-Barre Syndrome, Multiple Sclerosis, Amyotrophic Lateral Sclerosis)	12.1
ASTHENIA	(headache, weight loss/gain, dizziness, fainting/blackouts, fatigue, lethargy)	11.2
GASTRO-INTESTINAL	(pain, ulcers, diarrhea, bleeding, hemorrhoids, colitis, achalasia, regional enteritis)	10.9
REPRODUCTIVE	(decreaed sex drive, impotence, decreased fertility, miscarriages, sterility; genetic defects in offspring)	10.1
PULMONARY	(asthma, shortness of breath, infiltrates, chest pain, bronchitis, pulmonary hypertension, lung disease)	9.2
OPHTHALMOLOGIC	(conjunctivitis, visual loss, pterygium, blurred vision, light sensitivity, optic atrophy)	8.9
MUSCULO-SKELETAL	(arthritis, gout, fractures, stiffness, spasm, hernia, bone disease, strains)	8.1
CARDIO-VASCULAR	(hypertension, arrhythmias, myocardial infarction, peripheral vascular disease, heart problems)	7.5
GENITO-URINARY	(urethritis, stones, renal disease, prostatitis, epididymitis, testicular mass)	4.0
CENTRAL NERVOUS SYSTEM	(strokes, loss of memory, seizures, tremors, meningoencephalitis, speech impairment)	3.7
HEPATIC	(hepatitis, liver disease, gall-bladder disease, jaundice)	3.5

Table 3 (CONTINUED)

		PERCENT
PANCREATIC	(Diabetes Mellitus, pancreatitis, reactive hypoglycemia, increased amylase levels)	2.3
HEMATOLOGIC	(Pernicious Anemia, blood disorders, lymphnode disease, spleen disease, Polycythemia Vera)	1.4
COLLAGEN-VASCULAR	(Systemic Lupus Erythematosis, Rheumatoid Arthritis, Polymyositis, Sarcoidosis)	1.2
ALLERGIC	(allergic reactions)	0.9
FEVER	(low-grade fever, fever of unknown origin)	0.9
POISONING (LATERITIC SOILS)		0.3
PERIODONTITIS		0.3
AMYLOIDOSIS		0.3
HYPERTHYROIDISM		0.3

*NOTE: 13 CLAIMS ALLEGED EXPOSURE ONLY (WITHOUT SYMPTOMS) AS BASIS FOR COMPENSATION

Study design implications that can be drawn from these tables are limited due to the lack of knowledge concerning denominator data. Overall, the group of claimants exhibited a high frequency of readily identifiable disorders (e.g., dermatologic, psychiatric, and cancer). Further evaluation of the claims revealed that of the total number of claimants, 16.3%, had previous diagnoses of psychiatric disorders (20% of these diagnosed with schizophrenia).

Table 4 summarizes information on the USAF veterans as to general characteristics and alleged symptom category.

Table 4

HERBICIDE RELATED CLAIMS SUBMITTED BY USAF VETERANS BY SYMPTOM CATEGORY AS OF 30 APRIL 1979

Number of USAF Veterans: 28 (Mean age = 35.4 years)

Symptom	Percent
Psychiatric	50
Dermatologic	39
Reproductive	25
Peripheral Neuropathy	14
Cancer	7
Miscellaneous	7

The demonstrated lack of an easily identifiable symptom complex on review of the veteran claims clearly requires evaluation of individual symptoms. Therefore, a comprehensive questionnaire and physical examination is required.

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 1978 study by Hardell and Sandstrom in Sweden evaluated occupational exposure to chlorophenolic compounds in soft tissue cancer patients by a case-control design. They found an association between cancer and exposure, but methodologic problems have raised questions concerning the value of these findings.

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 method descriptions to verify his conclusions. The role of aflatoxin as an alternative cause of liver cancer was not addressed. His study was largely an empiric clinical study. 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. EPA concluded, however, that "for all its complexity, this analysis is a correlation analysis, and correlation does not necessarily mean causation." This report is currently 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 birth defects (neural tube abnormalities) and the use of 2,4,5-T herbicide.

Epidemiologic studies are continuing in Seveso, Italy. 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 (134) cleared rapidly. No evidence of significant hepatotoxicity, deranged porphyrin metabolism, or abnormal neurologic findings have been observed thus far. Growth and development of newborn infants

and children, immunological response, chromosome aberrations, the reaction to the challenges of infectious diseases, and the morbidity and mortality patterns of the study population have not been significantly altered by TCDD exposure to date. 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. 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 malformation rate is not significantly different than the rate in similar areas of Central Europe. Similarly, ascertainment and surveillance of spontaneous abortions after July 1976 is hampered by the lack of valid baselines for the pre-accident period. Chloracne appears to be the only significant adverse effect in the exposed population noted to date.

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 conclusions that there was no valid scientific evidence linking fetotoxicity, teratogenicity or carcinogenicity to 2,4,5-T/TCDD exposures in humans. The Human Exposure Working Group also concluded that there were no epidemiologic data associating TCDD with any long-term health effect 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. The Dow Chemical Company is currently analyzing data from a reproductive survey of the spouses of 2,4,5-T/TCDD exposed workers. 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.

These new studies, and the continuing evaluations of the Seveso, Italy, population, should 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 proposed goals for this study clearly mandate a broad comprehensive epidemiologic approach, incorporating "retrospective", cross-sectional, and prospective phases. The primary issue is time. Exposure to herbicides during the 1962-1970 time period may have initiated long-term health effects that may or may not be progressive. If such effects are detectable by specific past history, and are verified, there will be direct links to compensation. Current health status, as mirrored by the large number of recent VA claims, becomes of strong interest, because it might be confirmable by comprehensive physical examination. In the event both "retrospective" and cross-sectional methodologies yield indeterminant or weakly suggestive findings, it may be that sufficient time has not yet passed for substantial emergence of long-term health effects. This dictates a requirement for a prospective element to the study.

Many methodological shortcomings are inherent in each phase of this comprehensive study. To some extent, the classical deficiencies of each particular epidemiologic approach are compensated by the concurrent use of the other methods. For example, the low chance of identifying a relatively uncommon disease solely by the use of a cohort study is offset by the inclusion of the "retrospective" phase. The relatively quick feedback that can be attained from the "retrospective" and cross-sectional studies will serve to better define the prospective phase and will help to alleviate problems that arise in cohort studies as a result of changes in diagnostic criteria and methods with time. Nevertheless, there will remain many problems that will affect ascertainment of disease in all phases of the study. The problem with patient recall of antecedent events, the distortion of information by knowledge of the disease, as well as 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 jeopardize even the most comprehensive epidemiologic investigation. These and other pitfalls in study design will be discussed in more detail in Section VIII.

Since the study has three phases and confronts a health issue with undefined endpoints, including strong bias and political pressure with severe time constraints, the following design may represent the best overall framework for achieving validity. The design process is complex and in itself time dependent. All epidemiologic techniques used are time-compressed. Unique record searching systems within the Air Force, and computer and clinical capabilities, as well as bias and loss-to-study correctors, will work toward making this effort achievable.

B. Ascertainment of Exposed and Control Group Populations

(1) Exposed Group

Operation RANCH HAND personnel primarily flew C-123 aircraft in Vietnam during 1962-1970. Data from hand-compiled lists obtained through the RANCH HAND Association (a reunion organization), Air Force personnel computer entries, historical records and actual C-123 flight orders, place the estimated study population at 1000 (range 800-1200). Of those crewmembers now confirmed in the computer system, 25% are still on active duty, with the remainder being composed of retired or separated persons. An indepth search is being conducted of all organizational records stored at the Military Records Division, National Personnel Records Center (NPRC), St. Louis, Missouri, to identify all RANCH HAND participants. Detailed advertisements in active/retired military trade journals, VA publications, and local newspapers will be pursued in the near future to insure total ascertainment/identification of the exposed group. 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-3, Section XII).Because of the limited number of estimated RANCH HAND personnel (1000), no subsampling is planned in any phase of the study. All members will be invited to participate in all phases of the investigation.

(a) Known or Predicted Characteristics of the Exposed Group

All exposed aircrew personnel are males currently ranging in age from approximately 28-58 years. As the normal C-123 crew composition was one pilot and one copilot/navigator (both officers) and one spray equipment console operator in the rear of the aircraft (enlisted), the overall officer-enlisted ratio will be approximately 2:1. While almost all officers were Caucasian, approximately 10-14% of the enlisted men were Black. Attempts will be 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 personnel who were often dedicated exclusively to RANCH HAND operations. More extensive maintenance (secondary) was carried out by consolidated units at the base level, which were also responsible for nonRANCH 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

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HAND aircraft and these individuals can be identified by the mechanisms described above to identify the flight crew personnel. In 1965, flight line maintenance was performed by personnel of the centralized maintenance organization (secondary) and the individuals working on the RANCH HAND C-123s cannot be specifically identified 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 can again be readily identified. Thus, maintenance personnel directly assigned to RANCH HAND will be included in the study, but data from this group will be analyzed separately from the aircrew data. These complexities are summarized in Table 5.

Table 5

FEASIBILITY FOR IDENTIFYING AIRCRAFT MAINTENANCE PERSONNEL (TOTAL POPULATION) EXPOSED TO "HERBICIDE ORANGE"

Time	Primary Maint Personnel[1]	Secondary Maint Personnel[2]
Jan 1962-Jul 1964	Yes	No
Aug 1964-Dec 1966	Yes/No	No
Jan 1967-Apr 1970	Yes	No

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

Because of the significant combat hazard associated with low, slow flying missions, all early RANCH HAND crewmembers were elite volunteers (see Risk-Taking Bias, Section VIII). In fact, RANCH HAND crew members comprised one of the most highly decorated units during the Vietnam 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.

(2) Ancillary Study Groups (Non-RANCH HAND personnel)

Air Force handlers of herbicide drums in Vietnam were exposed to herbicides because of drum leakage. Advertisements similar to those proposed for the RANCH HAND personnel will be issued in attempts to define this population. As the drum handlers were ad lib participants, no personnel designator was assigned to these individuals, thus prohibiting computer tracking and identification. The population is unknown, but expected to be low (less than 200) as the majority of drum handlers were known to be Vietnamese. Additional study groups such as US Army personnel (officer and enlisted) who flew as observers, US Army helicopter crews, as well as experimental fighter-bomber spray personnel, may be injected into the study proper. Specific epidemiologic/clinical studies for these groups will be planned by a separate protocol following ascertainment; control group selection will be difficult or moot. It is intended that all data derived from the ancillary study groups will be subsetted for separate analysis; these data will be treated as anecdotal to the primary study.

(a) Known or Predicted Characteristics of the Ancillary Study Groups

All members of these groups are expected to be males, ranging in age from 28-68 years. The officer-enlisted ratio is estimated at 1:10. Approximately 10-18% of these populations are expected to be Black. Low numbers of respondents are expected (and with significant discordance to the above estimated characteristics due to socio-economic-race bias). Population at risk ascertainments are not possible.

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

A 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 best match variable concept (see below and Section VI, A). Many of the RANCH HAND aircraft were reconfigured for transport and insecticide missions. Thus, non-RANCH HAND crews responsible for these other missions, may have been exposed to Herbicide Orange residues in these aircraft. This group may not be truly unexposed to herbicides and therefore may not be an appropriate control population. The C-7 crewmembers have also been considered as a potential control group. This latter group, however, was comprised of only 1000 to 1200 individuals. Accordingly, aircrew members who flew C-130 aircraft in Vietnam during 1962-1970 will be selected as controls to the RANCH HAND aircrew population. Total ascertainment of this C-130 population is being conducted by computer selection for specific military flying organizations, foreign country service, etc. Over 2.3 million personnel records have already been scanned and the approximate C-130 sample size is 25,000 aircrew members. The C-130 flight line maintenance population will be ascertained

from personnel records by similar mechanisms, and will serve as the specific control population for the RANCH HAND maintenance personnel. The proportions on active duty, and non-active duty status are expected to parallel the patterns in the exposed group.

(a) Known or Predicted Characteristics of the Control Group

The normal crew composition of a C-130 is three officers and two enlisted personnel. The control group will be "pure" from the standpoint 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 probably possess similar lifestyle characteristics and socio-economic backgrounds, their overall combat morbidity/ mortality and resultant stress influences upon general health may be slightly less than 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 6.

(4) Matching Procedures and Rationale

Each member of the exposed group will be computer matched using four variables to a set of at least 10 C-130 control subjects. 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, (2) statistical intergroup comparisons may be made without normalization by four key variables known to effect symptom frequencies of interest, thus providing greater power for complex statistical testing, and (3) extremely close matching is feasible and necessary for some of the anticipated analyses of the physical examination findings. Matches will not necessarily be rigidly maintained throughout the data analysis phase, depending upon the particular analysis. It is apparent that following the match, both exposed and control populations will be very nearly identical with respect to the four influencing variables, and that in the event of frequent match breaks, stratification for a variable can be made with enough precision to ensure proper adjustment.

Matching will be conducted for (1) age, by year of birth, and closest month possible, (2) Air Force Speciality Code (AFSC) as an absolute match, (3) length of time spent in Vietnam, to the closest six month period, and (4) race (Caucasian versus non-Caucasian) as an absolute match. These variables are listed in priority order of the match sequence. Specific rationale for these variables is as follows: (1) many clinical symptoms and signs allegedly attributed to herbicide exposure (see literature review) can also be attributed to an aging effect, or to collateral diseases

Table 6

COMPARISON OF THE STUDY GROUP TO POSSIBLE CONTROL GROUPS BY

KNOWN AND ESTIMATED FACTORS

KNOWN FACTORS	STUDY GROUP	POSSIBLE CONTROL GROUPS		
	RANCH HAND C-123	Non-RANCH HAND C-123	C-7	C-130
POPULATION SIZE	800-1200	3000	1200	20,000-25,000
OFFICER/ENLISTED CREW RATIO	2:1	2:1	2:1	3:2
AIRCRAFT FUEL (AV-GAS)	YES (+JP-4)*	YES (+JP-4)*	YES	NO (JP-4)
OCCUPATIONAL HERBICIDE EXPOSURE	YES	YES/NO**	NO	NO
ESTIMATED FACTORS				
OCCUPATIONAL INSECTICIDE EXPOSURE	2+	1+ to 4+	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.

more commonly associated with advancing age, (2) AFSC controls specifically for officer-enlisted status (as well as crewmember or 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, (3) length of tour in Vietnam (measured in six month intervals, or actual flying hours, if feasible) controls for the generalized probability of combat morbidity, mortality, and for combat induced neuro-psychiatric disorders [additionally, length of tour may reflect effects related to intensity of alcohol consumption, drug consumption (chemoprophylactic or illicit), and degree of disease acquisition] and (4) race controls for difficulty in diagnosis of dermatitis, socio-economic background, etc. (note possible racial discordance for VA claimants).

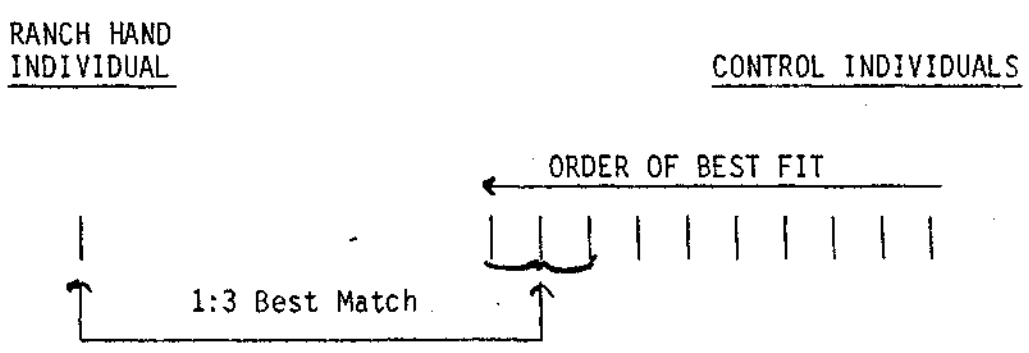
An intragroup comparison between health effects and an index of exposure to herbicides will be made in the exposed group. By using the length of time spent in Vietnam, as measured by the number of combat missions coupled to the preversus post-1965 time period when the concentration of TCDD contamination changed, a crude exposure index can be constructed, normalized, and tested.

(5) Study Group Selection Procedures

(a) Mortality Analysis

For the mortality analysis, the three "best-fit" controls will be selected for each exposed subject, regardless of current vital status (Figure 1). The current vital status of each exposed-control set will be determined, and their mortality experience will be followed throughout the duration of this study.

Figure 1. Selection Procedure for Mortality Analysis

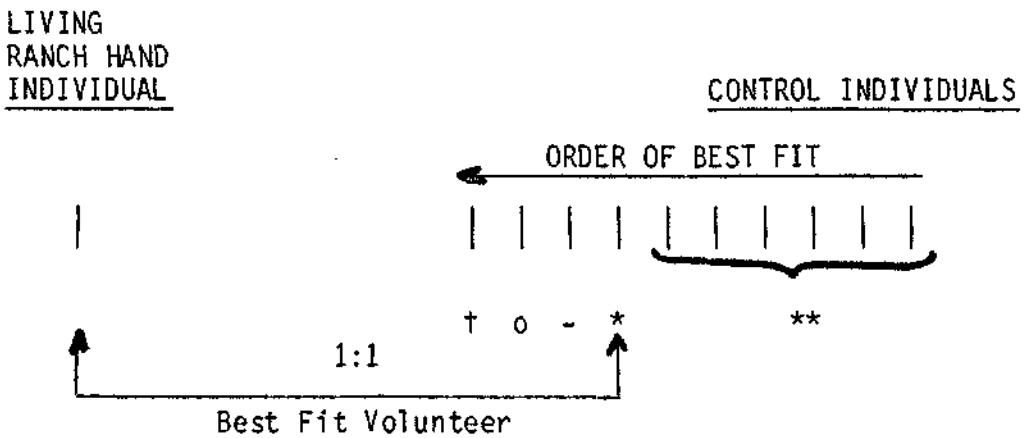


(b) Questionnaire, Physical Examination and Prospectus

In the questionnaire and physical examination phases of the study, a 1:1 match between each exposed living subject and his single "best-fit" (primary) control will be attempted. If

the primary control is deceased, unaccountable or unwilling to participate in the cross-sectional and prospective phases of the study, the next best control will be selected and so on until a volunteer is obtained (Figure 2). As control vital status and volunteerism should be independent of the priority matching sequence, many primary controls should enter the study. All replacement controls will be clearly identified for the purposes of subset analysis so that any inadvertent bias created by the replacement strategy can be assessed.

Figure 2. Selection Procedure for the Questionnaire, Physical Examination, and Prospectus



† Dead
o Unaccounted
- Unwilling
* Volunteer
** Replacement Candidates

C. "Retrospective" Phase

(1) Introduction

The term "retrospective" has been used generically in this discussion of the design protocol to address the event timing of selection/observation of the exposed and nonexposed groups, as well as the various means of tracing these groups to the present. More appropriately, the retrospective and prospective phases are components of a "nonconcurrent" prospective study used in the observation of a specially exposed group or industrial population starting from some date in the past. Therefore, the actual time of first exposure may span an eight-year period, and vary in intensity and duration from one RANCH HAND member to another. The availability of 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.

(2) Data Collection Methods

All exposed members and their matched primary controls will be given a comprehensive personal and family health questionnaire via telephone. The questionnaire (see Section XIII) will emphasize identification data, Vietnam tour history, dermatologic conditions, neuropsychiatric conditions, fertility aberrations, genetic defects in offspring, sensory defects, and personality factors, including assessments of risk-taking behavior. The questionnaire will be limited to a 30-45 minute telephonic interaction with participants,and it will take 10 to 12 months to complete all initial questionnaires on both groups. It may be necessary to conduct the questionnaire in two telephone sessions to minimize fatigue and maximize validity of response. The questionnaire will be "field-tested" on a group of 25 to 30 former Air Force pilots with Vietnam combat experience. Specific questions on the questionnaire will be directed to verifiable information, wherever possible. Inclusion of specific response verification and bias indicator questions (nonsense symptoms) have as yet not been included, since they are still under development. They will be added and appropriately sequenced immediately prior to the start of the study. Questionnaire data will be cross-linked and integrated with medical record information and physical examination findings. Questionnaire data from individuals not completing the study will not be discarded, but will be incorporated within the entire data base if statistically appropriate. Each participant will be asked to sign release forms so that all civilian health records, including those of dependents, can be reviewed as necessary. Federal health records on all family members on file in the NPRC will be retrieved. For retired members, and separated members with VA priviledges, all available VA medical records will be obtained. All retrieved medical records will be reviewed, scored, compared to questionnaire data for reliabililty, and then be entered into a repository system. Identified participants who are non-responsive to questionnaire will be pursed to determine status, disinterest, moribund state or death, etc. These individuals will be cross-referenced to other federal accounting systems in an attempt to achieve total ascertainment. Death certificates and autopsy reports will be retrieved on all dead exposed and matched control subjects for the mortality analysis. Birth/death certificates will be sought for all offspring, born subsequent to the study subject's Vietnam duty.

D. Cross-Sectional Phase

(1) Selection/Entry Criteria

A voluntary comprehensive physical examination will be offered to all individuals in both the exposed and primary control groups. The condition for entry into this phase will be completion of the baseline questionnaire. In the event that the

"best fit" control does not complete both the questionnaire and the physical examination, the next best fit will be selected, and so on, until a willing control is obtained. (See Figures 2,3) Statistical testing will be conducted by a variety of techniques on both questionnaire and examination findings (see VI, Statistical Methodology below). At the time of physical examination, an extensive indepth interview will be conducted. A standardized protocol will be used to insure comparability of inteview 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 during the interview as well.

(2) Physical Examination Parameters

A comprehensive physical examination will be conducted on all willing participants. The examination will be structured as outlined below and in Section XIV.

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

Dermatologic Examination

Urine Porphyrins
Urine Porphobilinogen
Delta-aminolevulenic Acid

Neuro-Psychiatric

Nerve Conduction Velocities
Psychological Battery

MMPI
WAIS
WRAT

Halstead-Reitan
Wechsler Memory Scale Subtests
Cornell Index

Reproductive Examination

LH, FSH, Testosterone
Semen Analysis

Neoplastic/Hepatic Examination

SGOT	Alkaline Phosphatase
SGPT	LDH (Isoenzymes if elevated)

Additional Studies (Individuals with abnormal history or examination)

Karyotyping	Hepatitis Antigens (A and B)
Additional Consultations as Required	Anti-Nuclear Antibody

Examinations will be performed in regional DOD medical facilities having dermatologic, neurologic and electromyogram/nerve conduction capabilities in the United States and overseas (Section XII, Figure A-2). A preliminary survey will be conducted to determine geographic location and willingness of subject to participate in physical examination. If participation rates can be improved by five percent or more, VA medical facilities will be requested to assist in performing physical examinations. This will generate better participation than if all examinations were conducted at a single location. Special Air Force authorization will be obtained to conduct such examinations on individuals separated from the service and informed consent forms will be obtained for nerve conduction tests. One hundred-twenty-five exposed subjects and an equal number of controls will be randomly selected to receive physical examinations at USAFSAM to minimize variability in nerve conduction testing. 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 and interns will not perform these examinations, and specialty trained neurologists and dermatologists will perform the appropriate portions of the examination. Clinical specimens will be forwarded to USAFSAM where most of the laboratory procedures will be conducted. The only laboratory procedures to be accomplished at the local facilities will be those which require fresh specimens (see Section XIV, D(5)). All laboratory tests will thus be subject to the same technology and 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.

Special contingencies will be made for unusal laboratory testing. Karyotyping of the individual and his family members will be performed 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 prospectus. 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 specificity. Appropriate specimens will be obtained from all participants, aliquoted, and preserved at -70°C for possible analysis in the future.

Physical examination and laboratory data will be placed in the member's 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. (Exceptions: In accordance with Air Force regulations, all active duty flying personnel and air traffic controllers found to have disqualifying defects will be temporarily "grounded" pending resolution; in accordance with federal regulations, all commercial airline pilots and air traffic controllers found to have disqualifying defects will be reported to the Federal Aviation Administration.)

E. Prospective Phase

(1) Study Adaptations

Following complete data analysis of the "retrospective" and cross-sectional phases, an adaptive or restrictive health survey will be developed and annually administered for five years. Similarly, a condensed physical examination profile that will achieve adequate sensitivity and specificity for prospective diagnosis will be developed. This adaptive physical examination by protocol will be applied to all prospective phase participants, and will be conducted at regional federal medical facilities every two years at government expense.

(2) Entry Criteria

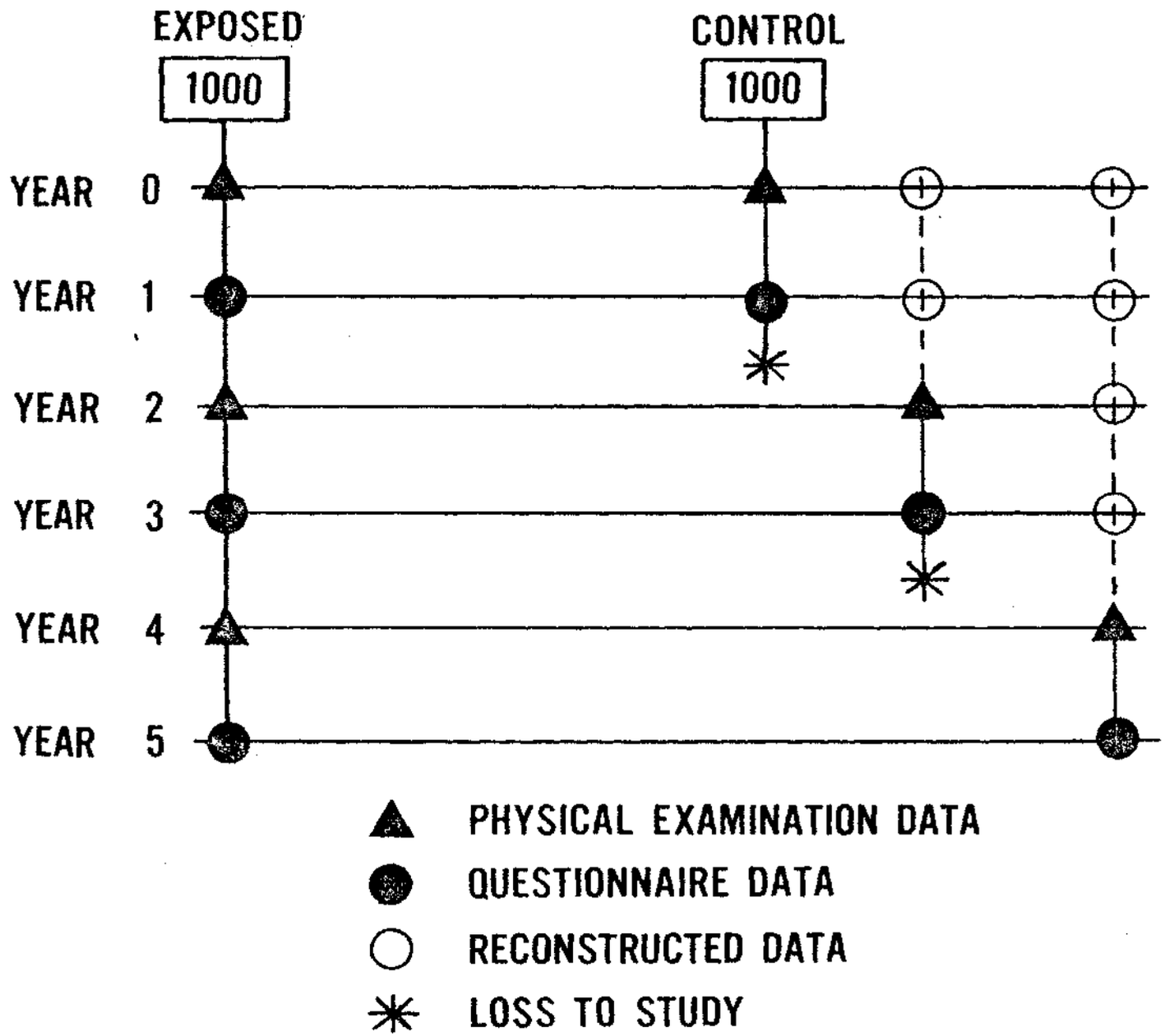
All exposed or control individuals completing the baseline questionnaire and physical examination will be entered into the prospectus; further continuation will depend upon the member's willingness/ability to participate in additional health surveys and condensed examinations.

(3) Loss to Study

At the initiation of the prospective phase loss of an exposed member will not be cause to cease surveillance of his matched control. In the event of a control loss, the next "best fit" match control will be brought to study (Figures 2 and 3), the comprehensive questionnaire will be administered, and a baseline physical examination performed. Medical data for the intervening years will be reconstructed from the questionnaire and interview responses. In all cases of loss-to-study, specific reasons for loss will be sought, 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 prospective

Figure 3

CONTROL REPLACEMENT FOR CROSS-SECTIONAL AND PROSPECTIVE PHASES



phase. The traditional approach to the problem of loss to study in the control group has been the use of multiple controls for each exposed subject in the anticipation that sufficient numbers of controls remain at the conclusion of the study to allow matched or stratified analysis. This replacement strategy will maintain the integrity of the matched design despite loss to study in the control group while minimizing the number of required physical examinations. As will be demonstrated in Section VI, F(a), a matched design provides greater statistical power than does random sampling.

(4) Study Length

The prospective phase is initially planned for five consecutive years. Results of the entire effort will be presented to a neutral scientific body. Their recommendation for continuance/discontinuance of the study will be forwarded to the Air Force Surgeon General for final decision.

F. Determination of "Disease"

(1) Introduction

Since this study is dealing with an unknown clinical endpoint, with unknown latency determination of disease state by statistical methodology is a prime scientific thrust of the investigation. From the literature, chloracne is the only recognized 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" becomes extremely difficult.

(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 "retrospective" and prospective phase. 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 prospective phase.

By the use of combinational and correlational analyses, statements about the probability of a disease state, a subclinical state, and over-reporting bias can be attempted. If the development of symptoms in the exposed group is positively correlated with physical findings, and this correlation is absent in the control group, a statement concerning the existence of a possible disease state can be made. By taking these possible combinations of observations and viewing them in the context of associated positive verifiers, negative bias indicators, and positive exposure index, the probability of over-reporting bias acting in these circumstances can be substantially reduced and, as a result, any statement concerning the existence of disease is strengthened. Similarly, if symptoms in the exposed group do not correlate with the development of findings, but are associated with positive laboratory results, a statement concerning the existence of a subclinical disease state can be made. On the other hand, if comparisons within the RANCH HAND group reveal a negative correlation between reported symptoms and the presence of abnormal physical signs, then an over-reporting bias and/or subclinical disease state is suggested.

Another method to assist in the determination of a disease state is the use of normalized exposure index and the application of regression techniques to the resulting curve. If there is a positive correlation between increased exposure and the presence of various abnormal physical signs and/or verifiable symptoms, then a symptom complex or disease syndrome is suggested. Factors suspected of altering the classical dose-response curve include cellular repair mechanisms and the release of TCDD from adipose tissue following weight loss. The addition of multivariate techniques to the regression analyses will strengthen statements about the presence of disease. Beyond these pair-wise and group comparisons, newer techniques of pattern recognition, such as Factor Analysis and Cluster Theory, are being considered in order to achieve a more automatic and objective analysis.

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.

G. Exposure Estimates

The exposure to 2,4,5-T herbicides by RANCH HAND personnel occurred almost daily. Anecdotal information suggests that many had direct skin contact which was repetitive over a long period of

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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. The available records on Operation RANCH HAND indicate that aircrews assigned to the project seldom had a "routine" work schedule or environment. Thus, numerous factors influenced the level of their herbicide exposure. Such factors included the length of tour, number of tours, crew position, number of herbicide dissemination missions, herbicides employed time to and from mission locations, and multiple routes of exposure (inhalation, ingestion and/or percutaneous absorption).

In an effort to determine the relative differences in exposure to herbicides within the C-123 aircraft, air dispersion studies are currently being planned in a C-123 configured with the same spray system as was used in South Vietnam. Data from such studies may permit a quantitative estimate of the relative levels of herbicide exposure received by the flight mechanics (console operators) and the cockpit crewmembers. Although industrial hygiene data are not available from defoliation operations during the Vietnam War, the Air Force did conduct extensive industrial hygiene monitoring programs during the dedrumming and incineration of Herbicide Orange during Project PACER HO (see Young, et. al., 1978). These monitoring data (e.g., breathing zone data) and recently conducted, but as yet unpublished data on percutaneous absorption of 2,4,5-T in humans during actual spray operations (Dow Chemical U.S.A., Midland MI, 1979), may permit more refined calculations of exposure estimates, when combined with data on characteristics of the C-123 aircraft, number of missions and crew position.

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VI. Statistical Methodology

A. Introduction

The design of the study is presented in schematic form in Figure 4. R' refers to the 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. Since C" may be 10 to 25 times larger than R', a subsample C' of C" may be constructed and matched to R' in a 3 to 1 manner (Carpenter, 1977; McKinlay, 1977). The control group C' will be matched to R' as closely as possible using: age, AFSC, Vietnam tour length, and race. C' will be constructed without regard to whether the individual is currently living or dead so that an assessment of mortality can be accomplished. Statistical aspects of this mortality analysis will be described in more detail below. If C' cannot be constructed from C" using 3 to 1 close matching, it will be constructed using stratified random sampling.

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

$$R = (1 - m_{R'})R'$$

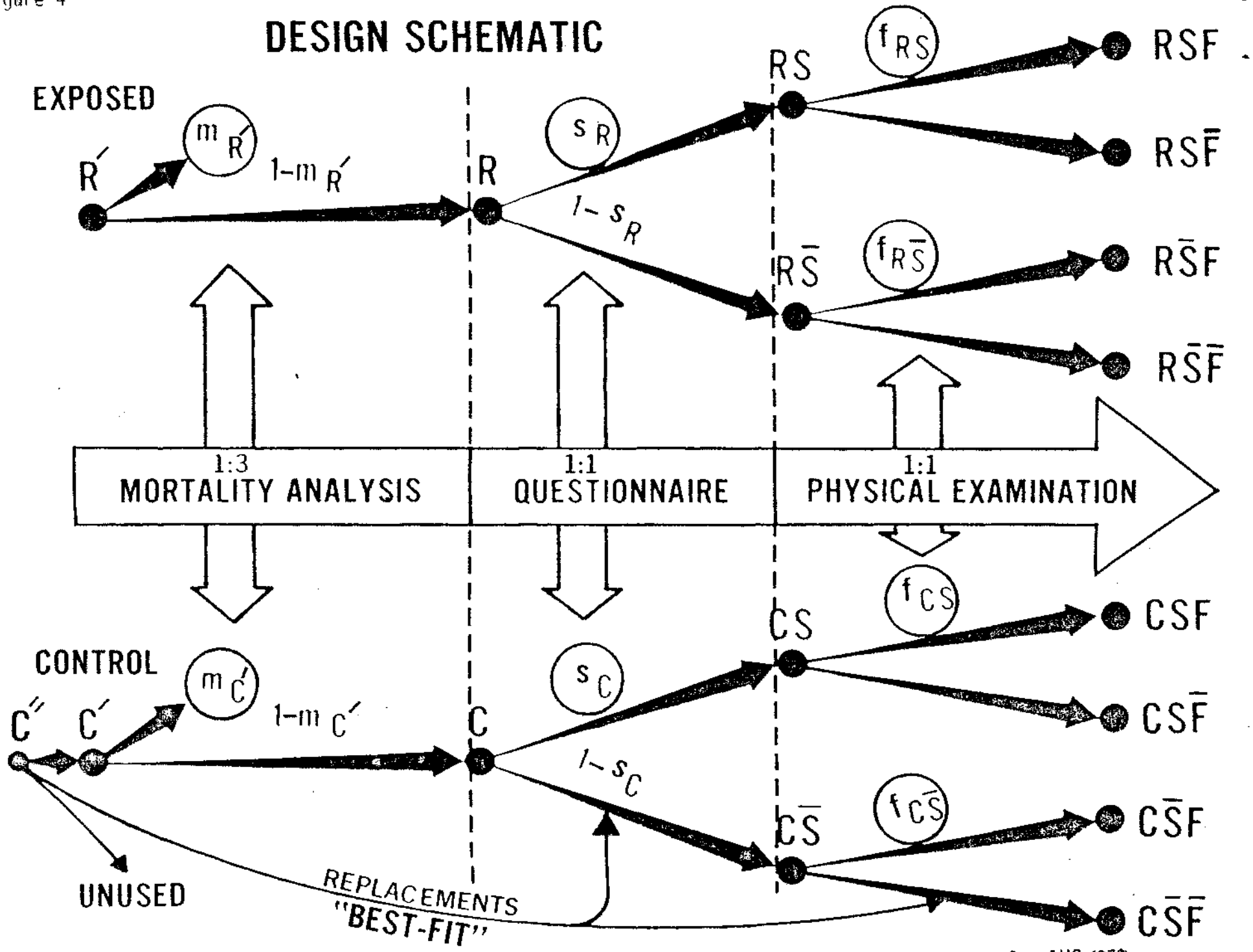
The questionnaire will provide data concerning specific symptoms and other findings in the R and C groups. Thus, various questionnaire finding rates in R, s_R, will be calculated and compared with the corresponding rates in C, s_C.

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 f_R and f_C for RANCH HAND and control groups respectively. Comparison of these rates is very important and details will be discussed below.

Let f_{RS} be the rate of physical findings among RANCH HAND personnel with findings by questionnaire and let $f_{R\bar{S}}$ 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 f_{RS} should be a larger rate than $f_{R\bar{S}}$. If f_{RS} is observed to be equal to or less than $f_{R\bar{S}}$, an interpretation of over-reporting may be warranted, although the possibility of subclinical disease is recognized. Rates f_{CS} and $f_{C\bar{S}}$ will also be estimated, and comparisons between f_{RS}, f_{CS}, $f_{R\bar{S}}$ and $f_{C\bar{S}}$ will be accomplished.

Figure 4


DESIGN SCHEMATIC
EXPOSED
R′
$m_{R'}$
$1-m_{R'}$
R
s_R
$1-s_R$
RS
f_{RS}
RSF
RS̄F̄
RS̄
$f_{RS̄}$
RS̄F
RS̄F̄
1:3
MORTALITY ANALYSIS
1:1
QUESTIONNAIRE
1:1
PHYSICAL EXAMINATION
CONTROL
C″
C′
$m_{C'}$
$1-m_{C'}$
C
s_C
$1-s_C$
CS
f_{CS}
CSF
CS̄F̄
CS̄
$f_{CS̄}$
CS̄F
CS̄F̄
UNUSED
REPLACEMENTS
"BEST-FIT"

During the questionnaire and physical examination phases of this study, only one control individual will be used for each RANCH HAND individual. If this best-matched control is unwilling to participate, the next best matched control will be used as indicated in Figures 2 and 3. These replacements will be carefully labelled for purposes of statistical comparison to the lost controls. Analysis without the replacements will also be accomplished, so that there will be no inferential loss from the use of replacements. If after the comparison it is appropriate to include replacements in the statistical analysis, power will be increased. Such a comparison may also provide insight into potential biases resulting from the use of this replacement strategy.

B. General Concerns

Before proceeding to statistical details regarding this design, three general areas of concern about the overall design will be discussed.

(1) Adequacy of the Control Group

Candidate groups comprising C", the set of all possible control crewmembers, include: C-130, C-7, and non-Ranch Hand C-123 crewmembers. Known and estimated factors relevant to these potential control groups and RANCH HAND personnel are listed and evaluated in Table 5. Considering the estimated factors, a subjective estimate from 0 to 4+ is provided. At the present time, no data have been found to suggest that the fuels involved in these aircraft have the capability to adversely effect health when the levels of exposure and exposure routes are considered. On the other hand, exposure to insecticide may be a significant confounding factor. Further, RANCH HAND personnel did have more combat involvement than the other groups thus far considered, and this stressful experience could exert a long term effect on morbidity and mortality rates in this group. Also, the fact that many RANCH HAND personnel volunteered for their hazardous duty suggests that this group may include individuals who are risk takers. This factor could inject significant bias into the study. For example, it is possible that risk taking behavior could be correlated with different patterns of disease; for instance, type A personality type could be more common among the intense, risk taking RANCH HAND personnel, thus increasing the incidence of cardiovascular disease. In relation to herbicide exposure, an increased accidental death rate among RANCH HAND personnel could well be an indication of herbicide induced peripheral neuropathy. Actual time spent in Vietnam could also be an important factor to control. The total time spent in Vietnam indicates a magnitude of stress imposed on the individual.

As indicated in Table 6 no available control group is ideal. Variations in risk taking behavior, and occupational insecticide exposure appear most important. Risk taking differences can be

approached using a risk taking scale and this will be discussed under mortality analysis and under analysis of questionnaire and physical examination data. Aircraft fuel differences may well be dismissed as an unlikely or nonexistent effect. Further literature search is also required as regards the possibility of an insecticide effect.

(2) Adequacy of Sample Sizes

The size of R' is approximately 1000 individuals. Without formal statistical analysis it should be quite 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 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, this study has little statistical power to define the relationship of herbicide to the rarer diseases.

(3) Misclassification

To understand the effect of misrepresentation on the estimate of relative risk and the odds ratio, let S stand for presence of a symptom, and $\bar{S}$ denote its absence. This misclassification may be represented as in Figure 5.

FIGURE 5

MISCLASSIFICATION

		ACTUAL STATUS		
		S	$\bar{S}$	TOTAL
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 misclassification, that is, when the sensitivity is the same among the exposed and non-exposed, and the specificity is the same among the exposed and non-exposed, the bias induced in the estimate of relative risk will be toward the null value. The situation may be summarized by Figure 6.

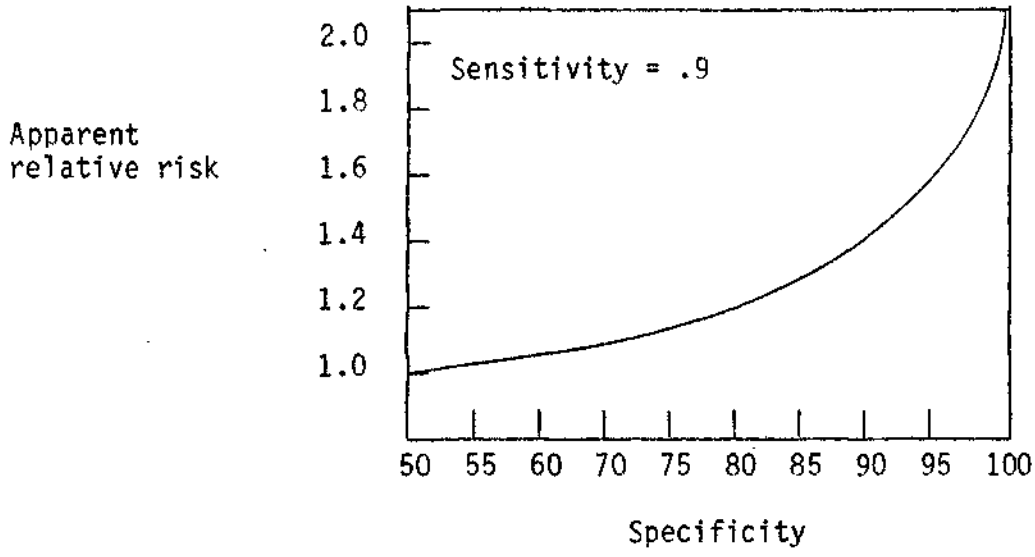
FIGURE 6

MISCLASSIFICATION IN RANCH HAND II

		ACTUAL 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 7 provides a graphic representation of how apparent relative risk varies as a function of sensitivity and 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 non-differential misclassification on the odds ratio is nearly as severe as that shown in Figure 7 for relative risk. A technique does exist for correcting the estimate of relative risk to account for misclassification, 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.

FIGURE 7
APPARENT RELATIVE RISK VERSUS
SPECIFICITY



If the misclassification 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).

(4) Nonresponse and Noncompliance

The prospective phase. Loss to follow up may occur for different reasons in the RANCH HAND group than in the Control group. In addition, this censoring may be related to the death experience, especially in the RANCH HAND group. For example, the disappearance of a RANCH HAND individual may be due to the effect of exposure, making loss to followup dependent on the death process. It should be noted that all currently available survival analysis techniques are founded on the assumption that censoring is independent of the death process, and all comparative tests require that the censoring mechanism operate in the same way in both groups considered. The effect of departure from the assumptions is not well understood.

The physical examination. Noncompliance will be a general problem in both the exposed and nonexposed groups. If the reasons for noncompliance are systematically different in the two groups, significant bias can result. For example, a number of RANCH HAND personnel may refuse to comply acting under advice from legal counsel. Noncompliant controls would not be likely to have this factor as a cause of nonresponse, but will probably be more motivated by reasons such as disinterest, or inability to take time from

work. RANCH HAND individuals motivated by legal advice or other similar reasons, may in fact be symptomatic, thus decreasing the number of positive findings in this study.

C. Analysis of Mortality Data

Considering the basic cohorts R' and C', individuals will be classified into three categories: alive, dead, unaccounted. If a large number of individuals of each group are unaccounted for, the study can obviously be severely biased. Thus, significant effort must be expended to reduce the unaccounted category as far 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 0.15, then an unaccountability rate of 0.01 is 6.6% of this mortality. Whatever the unaccountability rates, the pattern of unaccountability must also be compared between groups R' and C'. For example, the possibility of age differences or Vietnam tour length differences must be examined, particularly if the unaccountability rates are high. The following will discuss analysis of mortality under the assumption that low unaccountability rates have rendered the mortality analysis meaningful.

Two mortality analyses will be accomplished, one at the beginning of the study, using available mortality data on the basic matched cohorts C' and R'(1:3 ratio), and one several years later, using mortality data on C and R as it accumulates prospectively. Although the data bases for the two analyses will be different in many respects, the prospective data will be an update of the initial mortality data and the procedures described here and in Section E below can be used in both analyses. 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

	Ranch Hand			Controls		
Age Group	Person Years	Deaths	Death Rate	Person Years	Deaths	Death Rate
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 Proportionate Mortality Ratio (PMR) which is:

$$PMR = M \times 100$$

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

Classical standardized mortality ratios 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 deaths rates. Thus the concern is for a PMR greater than 100%. If a crude rate for controls, d_c, is calculated as

$$d_c = \frac{\sum_{j=1}^{k} P_{aj} r_{aj}}{\sum_{j=1}^{k} P_{aj}}$$

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

$$d_{RH} = Md_C.$$

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:

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

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 tour length, 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. These models, in the herbicide context would have the form

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

where

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

and where $\alpha_1, \beta_i, i=1,2,\ldots$ are coefficients to be estimated from the data. Testing for a group difference can be accomplished by estimating β_4 and 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) provide 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.

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

As discussed in section VI.B(1) above, it is postulated that RANCH HAND personnel may be properly characterized as risk takers. This risk taking behavior may be associated with increased mortality from a variety of causes. Let us first consider accidental death. If herbicide exposure has caused neuropathy in the RANCH HAND personnel, one should anticipate that this disability could increase the probability of accidental death. However, accidental death rates among RANCH HAND participants must surely be corrected for risk taking tendency. A method of accomplishing this correction for risk taking would be to employ a psychological instrument such as the Life Experience Inventory (Torrance, 1954) or the Sensation Seeking Scale (Zuckerman, 1972). Both control and RANCH HAND mortality could be corrected using these measures, with the resultant rates being perhaps less biased and, therefore, a better indicator of exposed versus control effect. The same argument may apply to death rates from cancer under the hypothesis that risk taking behavior would tend to increase the likelihood that a RANCH HAND individual would experience increased carcinogen exposure. The situation concerning mortality and morbidity from cardiovascular disease is noteworthy. RANCH HAND personnel in many instances volunteered for their particular duty. This step had the well known effect of improving officer evaluation scores. This volunteerism may be part

of a Type A behavior syndrome which has been correlated with enhanced atherosclerosis. Instruments for determining Type A behavior have been developed and these scores may be profitably used to correct cardiovascular mortality and morbidity rates.

D. Analysis of Questionnaire and Physical Examination Data

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

Dichotomous (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, tour length, 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. Returning to Figure 4, the eight rates m_R, m_C, s_R, s_C, f_{RS}, $f_{R\bar{S}}$, f_{CS}, $f_{C\bar{S}}$ fully characterize this study in a sense. In this figure, "Vertical comparisons," that is, m_R/m_C, s_R/s_C, f_{RS}/f_{CS}, $f_{R\bar{S}}/f_{C\bar{S}}$ are relative risks of central importance in defining herbicide effects. "Horizontal comparisons," that is f_{RS}/s_R, $f_{R\bar{S}}/(1-s_R)$, f_{CS}/s_C, and $f_{C\bar{S}}/(1-s_C)$ will enable interpretation of over-reporting and subclinical disease.

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

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

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. The reader will note that of course 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).

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, and with final testing using a paired difference "t" statistic.

TABLE 9

FORMAT CATEGORICAL REPRESENTATION OF RETINAL CHANGES

Retinal Category \ Age 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 LOG-LINEAR MODELS OF 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}

As indicated in section VI.E concerning the analysis of mortality data, risk taking behavior among RANCH HAND personnel could be correlated with changed mortality and morbidity patterns. Morbidity from cancer could be examined against a risk taking scale, and morbidity from cardiovascular disease could be corrected for personality type effect.

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 Vietnam, the number of miscarriages in spouses since exposure in Vietnam, the number of abnormal offspring since exposure in Vietnam. The study questionnaire will provide the number of miscarriages, abnormal offspring and total number 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.

E. Survival Analysis

This section extends and complements sections C and D. The defining common attribute of the techniques discussed in this section is that they deal with events which (a) correspond to categorical changes in health status, and (b) occur at definite and observable times. These methods may, therefore, be applied to studies of mortality (as the name "survival analysis" implies) as well as to studies in morbidity.

Survival analysis without covariates. The first step in the statistical analysis of survival data is descriptive, i.e., 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). However, the product-limit estimator of Kaplan and Meier (1958) may be preferred due to its intrinsic properties and its relationship to more refined methods.

The failure time distribution is the function $F^o(t)$ which provides the probability of death at or before time t in the study. The Kaplan-Meier estimator of $F^o(t)$ is $\hat{F}^o(t)$ where

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

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 ith study individual in $D(t)$. This product-limit estimator of Kaplan and Meier is maximum likelihood in the class of all possible failure time distribution functions.

Assuming that failure time distributions have been calculated for RANCH HAND individuals and controls, the next question concerns testing the null hypothesis of equality between the distributions. When only two such distributions are being compared, one may use the nonparametric procedures generalizing Wilcoxon's statistic proposed by E. Gehan (1965a, b) and discussed by N. Mantel (1967). When more than two such distributions are being compared, one may use the nonparametric procedure generalizing the Kruskal-Wallis statistic proposed by N. Breslow (1970).

Survival analysis with covariates. These methods allow adjustment of mortality rates or morbidity rates using covariates such as age, race, Vietnam tour length, 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 that 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 ith 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 ith individual. It is readily shown that the failure time distribution $F_i^o(t)$ is given by:

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

From this last equation it follows that h_i and F_i^0 are transforms of each other, whence the dependence of F_i^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 ith 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). The basic model for hazard is:

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

where ξ and η are "log-relative risks". It is shown in J. Frank (1977) that 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).

F. Statistical Power

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 study makes use of the entire known RANCH HAND population (and excludes ancillary exposed groups for reasons previously cited); it 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 considerations. Hence, considerable effort has been made to correct loss to study issues (via resampling without replacement and techniques to induce participation) and to use the most powerful statistical design concepts. Essentially all animal and human studies concerning herbicide suffer from a lack of adequate consideration of study power. While the present study is not a powerful one against less common disease states as already discussed, it is obviously important nonetheless to exactly specify just what the study can and cannot accomplish. The following presents a preliminary analysis of study power for the case of continuous and dichotomous variables expected from the study.

(1) 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: $\alpha=0.05$, $\sigma_c/\mu_c=0.1$, $\gamma = \mu_{RH}/\mu_c$

		Power = $1-\beta$	
R	γ	n=180	n=450
.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.

(2) 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 DICHOTOMOUS VARIABLE CASE AS A FUNCTION OF EFFICACY OF PAIRED DESIGNS

				POWER = 1- β					
P_1	P_2	Rel. Risk	r	n= 160	n= 200	n= 250	n= 300	n= 350	
.05	.01	5	0	.71	.78	.84	.89	.92	*
.04	.01	4	0	.56	.64	.72	.79	.84	
.03	.01	3	0	.40	.45	.51	.57	.61	
.10	.05	2	0	.54	.61	.69	.76	.81	
.20	.10	2	0	.80	.86	.92	.95	.95	
.05	.01	5	.1	.65/.02	.82/.033	.89/.029	.94/.038	.96/.032	**
.04	.01	4	.1	-	.54/.020	.72/.033	.79/.029	.87/.038	
.03	.01	3	.1	-	-	.38/.020	.55/.033	.68/.046	
.10	.05	2	.1	.60/.058	.67/.054	.76/.055	.77/.036	.85/.048	
.20	.10	2	.1	.81/.036	.92/.056	.94/.043	.96/.038	.98/.046	

*α = .050
**α as indicated

In this figure, 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 p_1, while p_2 is the probability of the disease among the controls. Relative risk is the ratio p_1/p_2. 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 350 pairs (700 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 increased 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.

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

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

where

p = the probability of a complicated coronary lesion

x = age scaled linearly so that x = 0 is equivalent to 38 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 figure 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.

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	$\gamma = \beta$ Power Neglecting Pairing	$\gamma = \beta$ Power With Pairing	$\gamma = .8\beta$ Power Neglecting Pairing	$\gamma = .8\beta$ Power With Pairing
100	.93	.93	.64	.53 (α = .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

G. Multivariate Analysis

Some questionnaire and physical examination data naturally fall into groups; for example, fertility/reproduction data, liver function tests, cardiovascular examination tests. In these cases, multivariate analysis may be in order. When the response variables are continuous, they will be analyzed by the well known multivariate extensions of the generalized linear model.

The general approach to multivariate analysis of polytomous data considers all classification factors and all variables as "factors" in a multi-way contingency table. Log-linear models as described above for polytomous data will be employed where appropriate.

H. Indices and Estimates of Exposure

Exposure estimates can be used to sharpen a statistical analysis and can be helpful in summarizing responses. In this discussion, two estimates will be considered: one related to Vietnam herbicide exposure, and another related to domestic (US) herbicide exposure independent of Vietnam experience.

Vietnam herbicide exposure. In the above discussion of statistical methodologies, exposure variables appeared. In the logistic formula on page VI-9, the variable E was shown which could be either dichotomous, polytomous or continuous. In the use of logistic functions

to discuss study power, the exposure variable was taken as dichotomous. If a polytomous or continuous exposure variable E is constructed, significant sharpening of the study analysis would be accomplished. For example, biases in this study could lead one to suspect that differences between RANCH HAND personnel and controls were in fact due to factors other than a herbicide effect. If however, in addition to differences between RANCH HAND personnel and controls, one was able to show a regression of mortality and/or morbidity on an exposure index E, the case for a bona fide herbicide effect would be firmer. The reconstruction of exposures is discussed in Section V, G.

Domestic herbicide exposure. Individuals in both the RANCH HAND and control groups will have had varying exposure to herbicide in the United States. Particularly, individuals from specific farming and/or foresting areas, may have had and continue to have a significant background exposure. Data on place of residence and information concerning home practices (gardening etc.) could be used to build a background exposure index E_b. In lieu of constructing this index, one can hope that randomization would "even-out" background exposure between RANCH HAND and control groups, however, good statistical practice would seem to require that such randomization be in fact tested.

I. Next Steps

This statistical protocol is evolving as more is learned about the cohorts to be studied. The next weeks and months will be the occasion for the examination of several issues not addressed above or only touched upon. There must be further consideration of RANCH HAND personnel as risk takers. Also, there must be further assessment of bias due to selective participation in the study and further analysis of the replacement concept. In the analysis of mortality, questionnaire and physical examination data, more attention will be paid to the construction of meaningful exposure and disease indices.

VII. Data Repository

Throughout the 6-year 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 on 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.

Individual data bits and their sources are as follows:

(1)	Questionnaire	a. Initial (telephone) b. Indepth interview (personal and telephone) c. Prospective (telephone)
(2)	Psychological Battery	a. Initial b. Prospective
(3)	Physical Examination	a. Initial b. Prospective
(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

The computer software for the data analysis phase will be prepared to assure proper data conversion, quality control and standardization of test measurements. Quality control areas will include verification of identification data, range checks, and identification/correction of ambiguous or conflicting data. The repository capability of this investigation will allow complete computer files on the exposed/control populations with potential momentary recall.

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., PMR) 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

Unprecedented study designs forced by unprecedented occurences of occupationally related medical complaints require novel approaches, and reorientation and standardization of thinking; all of which require an effective Peer Review system. 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 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 attempting to keep 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.

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 early RANCH HAND

operation casts doubt on the adequacy of this basic matching as an attempt to control for the psychological effects of combat stress. 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). These models will be adapted for use throughout all phases of the study. The classical model of field dependence/independence will be used to assess the group effect in this area.

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. A "pending-retirement phenomenon" occurs 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 reponses and the physical examination results will be conducted. All telephone 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. 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 predicated and coupled to a bias estimate.

E. Interview 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

An extensive interviewer training program will be conducted in order to limit the effects of interview bias. The Survey Research Center of the University of Illinois and the Center for Disease Control, Venereal Disease Training Branch, Atlanta, Georgia, will assist in this effort. The training will concentrate on techniques to elicit sensitive personal and medical information in an accurate manner, while minimizing discomfort to the subject and the interviewer. Quality assurance methodology and information verification techniques will also be included in the training. Interviews will be randomly monitored by the supervisor in an unannounced and undetectable manner. For particularly sensitive questions (e.g. illicit drug usage), randomized response techniques (coin flip method) will be used, recognizing that responses will be valid on a group basis only.

F. Political Implications

(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 political 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, monumental 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 dilution of the scientific credibility of this effort by politically motivated 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. Such issues will be clearly presented to appropriate peer review agencies for comment. If studied, ancillary groups will be analyzed separately from the main study group and reported anecdotally.

G. Loss to Study

(1) Problem

Loss to study in the RANCH HAND group poses 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 lost worktime, 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 resampling from the best-fit matches from the C-130 population (Figure 3). Consequently, additional decrements in statistical power may not result from losses in this group. However, significant losses in the exposed group will have irreparable adverse effects on the power of the statistical analyses. The estimated allocation of participants in this study is shown in Section XII, Figure A-3. It is estimated that the response rate of the accessible, identified exposed group will be 70% in both the initial questionnaire and the physical examination phases of the study. This is expected to occur despite great efforts to keep the questionnaire at an acceptable length, to coordinate questionnaire administration with the subject's personal schedule, and to make the questions as innocuous as possible. It is also estimated that only 80% of those who respond positively to the opportunity for physical examinations will actually present themselves for examination.

(2) Corrective Measures

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 encouraged to reconsider their initial decisions. Design considerations have been made to minimize loss to study in both the exposed and control populations. If necessary, non-DOD federal hospitals in the United States and overseas will be used to facilitate the ease of obtaining physical examinations, and thus participation in the cross-sectional and prospective study phases will be increased. Overall, it is felt that physical examination variances due to slight differences in technique between hospitals and physicians will be less damaging to the validity of the study than the effects resulting from attempts to conduct all of the examinations at a single facility, i.e., examination at a single facility would reduce participation rates, and therefore would severely compromise the overall statistical power of the study. Nerve conduction studies are likely to be the most sensitive to inter-facility variability. As a result of this, a randomized subset of exposed and control subjects will be tested at USAFSAM and compared to the other centers.

H. Statistical Power Limitations

(1) Problem

As discussed above, statistical power considerations are heavily dependent on loss to study rates. Since the design of the study is limited by the small exposed population, statistical power for identifying the relative risk of an uncommon disease or symptom-complex (<1/100) is very low (<.50). This study will, to a greater extent, be able to detect increased risks only 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 Homberger, 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 within the constraints imposed on 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 reported human effects of TCDD exposure appear to fall within the capabilities of this study design (e.g., peripheral neuropathy, neuro-psychiatric effects, and liver dysfunction).

In general, with respect to statistical power, continuous data on relatively low numbers fair much better than either categorical or dichotomous data. Consequently, a concerted effort will be made to obtain physical examination data in a scored and/or continuous manner.

I. Variablility of Procedures

(1) Problem

The variance of physical examination findings from technique differences 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, similar equipment, and training. Most laboratory procedures will be conducted centrally at the USAFSAM, and quality control will be stressed at all times. A randomized subset of the exposed and control groups will receive their physical examination at USAFSAM in order to eliminate variability in the nerve conduction studies. Group size will be determined by statistical power calculations.

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 many of these same aircrewmembers when RANCH HAND duties permitted their temporary assignment to mosquito/malaria control units. 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 auxilliary jet engine boosters for added power on takeoffs and 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 a significant confounding factors.

IX. 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 : Retrospective Study, July 1981; Cross-Sectional Study, October 1981; and Prospective Study, April 1986. 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.

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XI. SELECTED BIBLIOGRAPHY (Key References)

GENERAL REFERENCES:

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 Techincal Report No. 78/001. Coordination of epidemiological studies on the long-term hazards of the chlorinated dibenzo-dioxins/chlorinated dibenzo-furans. 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.

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-trichloro-phenoxyacetic 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.

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

Grunow, W. and C. Bohme. 1974. Uber den stoffwechsel von 2,4,5-T and 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 ^{14}C-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.

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-trichlorohenoxyacetic 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.

PHARMACOKINETICS OF TCDD

Allen, J. R., J. P. Van Miller and D. H. Norback. 1975. Tissue distribution, excretion and biological effects of [^{14}C] 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.

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. Pharmacodyon. 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.

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. Cytogentic 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: enviromental contaminant and molecular probe. Fed. Proc. 35(12):2404-2411.

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.

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. Crimaudo, 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.

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.)

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.

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. Brodkin, and I. L. Applebaum. 1964. Industrially acquired porphyria. Arch. Dermatol. 89:793-797.

Brandt, M. R. 1971. Herbatoxforgiftning, en Kort oversigt og et nyt tilfaelde. (Herbatox poisoning, a brief review and a report of a new case). Ugeskrift for Laeger 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.

EPIDEMIOLOGIC STUDIES

Alfred, J. E. (Chairman). September 1978. Report on the consultative council on congenital abnormalities in the Yarram District (Australia). Austalian Commission on Public Health. Document No. 47-12004/78, Government Printing Office, Melbourne, Australia. 55p.

Hardell, L., and A. Sandstrom. 1978. Maligna masenkymala mjukdelstrumorer och exposition for fenoxisyror eller klorfenoler. (Malignant mesenchymal soft-tissue tumors and exposure to phenoxy acids or chlorophenols.) Lakartidningen 75(40):3535-36. (Swedish)

Homberger, 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. 1970, Revised 1974. Health of employees exposed to 2,4,5-T. Dow Chemical Co., Midland, Michigan. Mim. Unpublished data, 19 p.

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.

Tung. T. T. 1973. Le Cancer primaire du foie au Vietnam. (Primary cancer of the liver in Vietnam.) Chirurgie 99(7):427-36. (French).

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.

QUESTIONNAIRE DEVELOPMENT

Waters, C. W., R. Ambler, and L. K. Waters. 1976. Novelty and sensation seeking in two academic training settings. Educ. Psychol. Meas. 36:453-457.

Zuckerman, M. 1974. The sensation seeking motive. P 79-148. In Progress in Experimental Personality Research. B. A. Maher (Ed.). Academic Press, New York.

Zuckerman, M., E. A. Kolin, L. Price and I. Zoob. 1964. Development of sensation-seeking scale. J. Consult. Psychol. 28:277-482.

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.

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 in 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.

Kaplan, E. and P. Meier. 1958. Nonparametric estimation from incomplete observations. J.A.S.A. 53:457-581.

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.

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.

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.

Zuckerman, M. 1972. Manual and research report of the sensation seeking scale. Department of Psychology, University of Delaware, Newark, Delaware.

XII. APPENDIX

TABLE A-1	SUMMARY OF 2,4-D; 2,4,5-T and TCDD ANIMAL STUDIES
TABLE A-2	"SYMPTOM COMPLEX" DERIVED FROM LITERATURE REVIEW OF CASE STUDIES EXPOSED TO 2,4-D; 2,4,5-T AND/OR TCDD
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
FIGURE A-1	2,3,7,8 -TETRACHLORODIBENZO-P-DIOXIN (TCDD)
FIGURE A-2	LOCATION OF DOD MEDICAL FACILITIES WITH CAPABILITY TO PERFORM RANCH HAND II PHYSICAL EXAMINATIONS
FIGURE A-3	ESTIMATED IDENTIFICATION/ PARTICIPATION OF RANCH HAND POPULATION

TABLE A-1

	2,4-D	2,4,5-T	TCDD
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	ANOREXIA	WEIGHT LOSS
	WEIGHT LOSS	ATAXIA	INVOLUTION OF THYMUS
	MUSCULAR WEAKNESS	G.I. INJURY	ALOPECIA
	IRRITATED G.I. TRACT	LIVER CONGESTION	EPITHELIAL CHANGES
	MINOR LIVER INJURY	KIDNEY CONGESTION	LIVER LESIONS (VARIABLE)
	MINOR KIDNEY INJURY		HYPOTHYROIDISM
	MINOR LUNG CONGESTION		
EMBRYO TOXIC DOSE	APPROACHES TOXIC LEVEL	APPROACHES TOXIC LEVEL	MARKEDLY BELOW TOXIC MATERNAL LEVELS
TERATOGENICITY	QUESTIONABLE; WEAK AT BEST	*LOW INCIDENCE ONLY IN MICE (CLEFT PALATES & DILITATED RENAL PELVIS)	SPECIES VARIATIONS: YES MICE NO RATS
CARCINOGENICITY	QUESTIONABLE WEAK AT BEST	ONE STUDY: YES NUMEROUS STUDIES: NO	EPITHELIAL CHANGES IN PRIMATES: YES IN RATS

*TCDD CONTAMINATION OF 2,4,5-T HAS BEEN SHOWN TO BE A CONTRIBUTOR TO TERATOGENIC EFFECT IN MICE

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TABLE A-2 "SYMPTOM COMPLEX" DERIVED FROM LITERATURE REVIEW OF CASE STUDIES

EXPOSED TO 2,4-D; 2,4,5-T AND/OR TCDD

2,4-D	2,4,5-T (+ TCDD)	TCDD
	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		
CSF PROTEIN ALTERATIONS		HYPOTHYROIDISM
CONVULSIONS		HEARING/SMELL 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

NEURO-PSYCHIATRIC ABNORMALITIES

AESTHENIA	PERIPHERAL NEUROPATHY
ANXIETY	HYPOREFLEXIA
DEPRESSION	WEAKNESS
FATIGUE	PARESTHESIAS
APATHY	EXTREMITY NUMBNESS
LOSS OF DRIVE	MYALGIA
LIBIDO	GAIT DISTURBANCE
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	RENAL DYSFUNCTION
INCREASED CHOLESTEROL AND TRIGLYCERIDE	PROTEINURIA
	DECREASED OUTPUT
INCREASED LIVER FUNCTIONAL TESTS	TUBULAR DEGENERATION
	GLOMERULAR DEGENERATION
	RENAL GLUCOSURIA
GI DISTURBANCE	**CARDIAC DISTURBANCE**
NAUSEA	BRADYCARDIA
VOMITING	TACHYCARDIA
DIARRHEA	ATRIAL FIBRILLATION
GASTRITIS	
ABDOMINAL PAIN	

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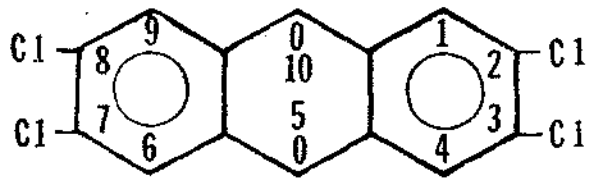
2, 3, 7, 8-TETRACHLORODIBENZO-p-DIOXIN (TCDD)



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

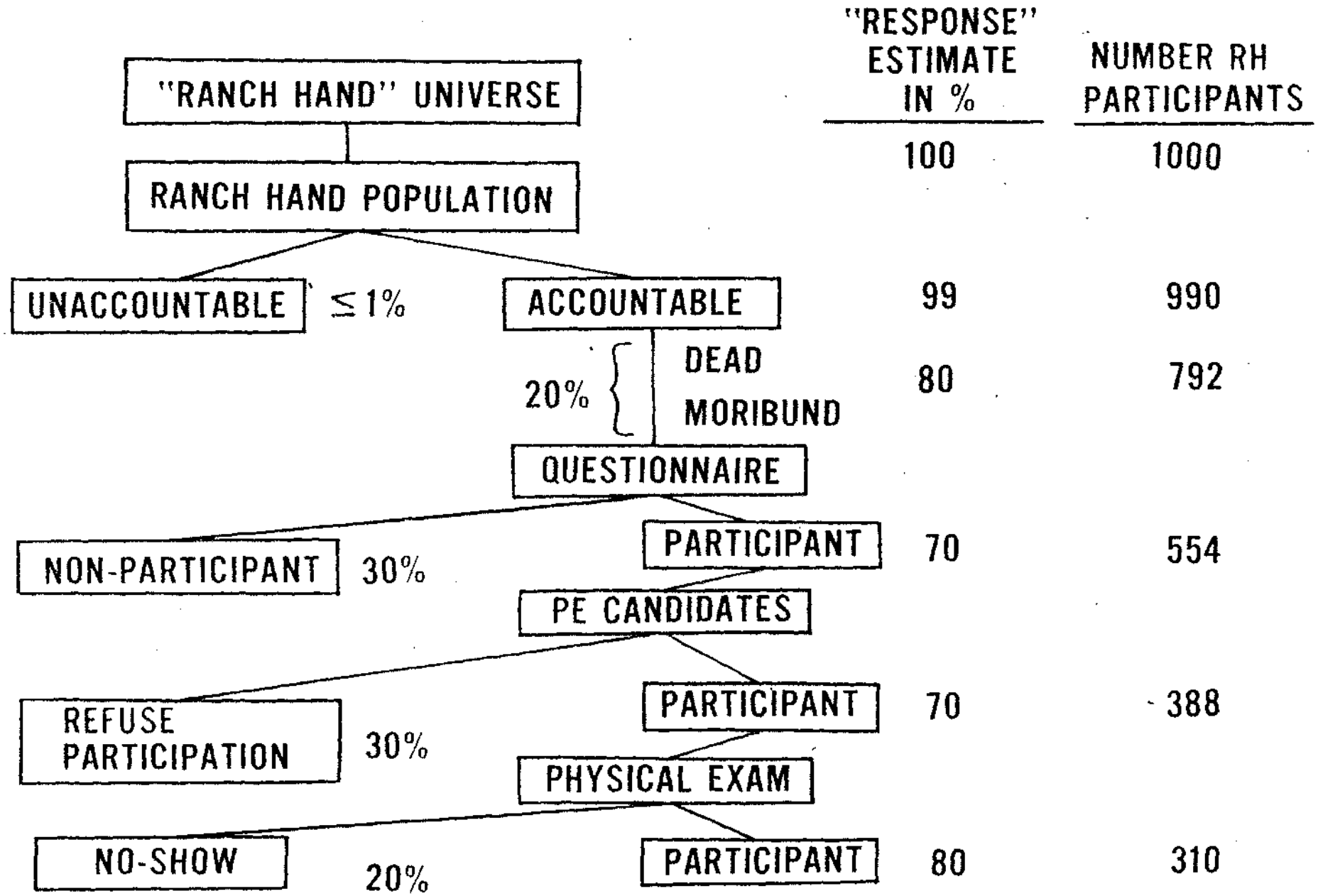
ORTHO-DICHLOROBENZENE	1.40
CHLOROBENZENE	0.72
ORANGE HERBICIDE	0.58
BENZENE	0.57
CHLOROFORM	0.37
ACETONE	0.11
METHANOL	0.01
WATER	2×10^{-7}

Figure A-2

LOCATION OF DOD MEDICAL FACILITIES WITH CAPABILITY TO PERFORM RANCH HAND II PHYSICAL EXAMINATIONS

Figure A-3

ESTIMATED IDENTIFICATION/PARTICIPATION OF RANCH HAND POPULATION



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XIII. QUESTIONNAIRE

USAFSAM CODE _____

XIII. Ranch Hand II - Draft Questionnaire

INTERVIEWER _____

DATE _____

TIME STARTED _____

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PERSONAL IDENTIFICATION:

1. YOUR NAME: _____ (Last First M.I.)

2. DATE OF BIRTH: YR MO DAY ☐☐ ☐☐ ☐☐

3. CURRENT ADDRESS: _____ _____ _____ _____ (Number Street City State Zip)

4. SSAN: ☐☐☐ ☐☐ ☐☐☐☐

5. PREVIOUS SERVICE NUMBERS: ☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐

6. PHONE NUMBER (WORK): AC ☐☐☐ ☐☐☐ ☐☐☐☐ (HOME): AC ☐☐☐ ☐☐☐ ☐☐☐☐

7. RACE/ETHNIC GROUP: CAUCASIAN ☐ BLACK ☐ MEXICAN AMERICAN ☐ ORIENTAL ☐ OTHER ☐ (Specify) _____

8. MILITARY STATUS: ACTIVE DUTY ☐ RETIRED (YR) ☐ SEPARATED (YR) ☐

9. YEARS OF EDUCATION: LESS THAN 12 ☐ 12 ☐ 13-14 ☐ 15-16 ☐ 17+ ☐

10. WHICH OF THE FOLLOWING WORDS BEST DESCRIBES YOUR PRESENT STATE OF HEALTH:

a. VERY POOR ☐ b. POOR ☐ c. FAIR ☐ d. GOOD ☐ e. EXCELLENT ☐

11. Where are your Air Force medical records now? _____

12. Where are your dependents' Air Force medical records now? _____

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13. MEDICAL PROBLEMS CODE	NO	YES PRIOR TO VIETNAM DUTY	DURING VIETNAM DUTY	AFTER RETURN TO US	NOW	DID YOU SEEK MEDICAL ADVICE? YES	NO	WERE YOU HOSPITALIZED FOR IT? YES	NO	WHAT WAS THE CAUSE?	FOR USAFSAM USE ONLY
a. HEADACHES	☐	☐	☐	☐	☐	☐	☐	☐	☐		
b. HOARSENESS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
c. SKIN RASH											
(1) EARS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
(2) EYES	☐	☐	☐	☐	☐	☐	☐	☐	☐		
(3) TEMPLES	☐	☐	☐	☐	☐	☐	☐	☐	☐		
(4) CHEEKS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
(5) NECK	☐	☐	☐	☐	☐	☐	☐	☐	☐		
(6) ARMS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
(7) LEGS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
(8) CHEST	☐	☐	☐	☐	☐	☐	☐	☐	☐		
(9) BACK	☐	☐	☐	☐	☐	☐	☐	☐	☐		
(10) GROIN	☐	☐	☐	☐	☐	☐	☐	☐	☐		
d. DEPRESSION	☐	☐	☐	☐	☐	☐	☐	☐	☐		
e. ANXIETY	☐	☐	☐	☐	☐	☐	☐	☐	☐		
f. APATHY	☐	☐	☐	☐	☐	☐	☐	☐	☐		

	NO	YES: PRIOR TO VIETNAM DUTY	YES: DURING VIETNAM DUTY	YES: AFTER RETURN TO US	YES: NOW	DID YOU SEEK MEDICAL ADVICE? YES	NO	WERE YOU HOSPITALIZED FOR IT? YES	NO	WHAT WAS THE CAUSE?	FOR USAFSAM USE ONLY
g. LOSS OF DRIVE	☐	☐	☐	☐	☐	☐	☐	☐	☐		
h. EMOTIONAL INSTABILITY	☐	☐	☐	☐	☐	☐	☐	☐	☐		
i. MUSCULAR WEAKNESS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
j. HYPOREFLEXIA	☐	☐	☐	☐	☐	☐	☐	☐	☐		
k. PARESTHESIAS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
l. MYALGIA	☐	☐	☐	☐	☐	☐	☐	☐	☐		
m. STYLE OF WALKING	☐	☐	☐	☐	☐	☐	☐	☐	☐		
n. MILD PARESIS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
o. FATIGUE	☐	☐	☐	☐	☐	☐	☐	☐	☐		
p. DECREASE IN LEARNING ABILITY	☐	☐	☐	☐	☐	☐	☐	☐	☐		
q. DECREASED MEMORY	☐	☐	☐	☐	☐	☐	☐	☐	☐		
r. UNDESIRED WT LOSS (10 lbs)	☐	☐	☐	☐	☐	☐	☐	☐	☐		
s. ANOREXIA	☐	☐	☐	☐	☐	☐	☐	☐	☐		
t. LUNG DISEASE	☐	☐	☐	☐	☐	☐	☐	☐	☐		
u. DIZZINESS	☐	☐	☐	☐	☐	☐	☐	☐	☐		

	NO	YES: PRIOR TO VIETNAM DUTY	YES: DURING VIETNAM DUTY	YES: AFTER RETURN TO US	YES: NOW	DID YOU SEEK MEDICAL ADVICE? YES	DID YOU SEEK MEDICAL ADVICE? NO	WERE YOU HOSPITALIZED FOR IT? YES	WERE YOU HOSPITALIZED FOR IT? NO	WHAT WAS THE CAUSE?	FOR USAFSAM USE ONLY
v. LOSS OF CONSCIOUSNESS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
w ACNE	☐	☐	☐	☐	☐	☐	☐	☐	☐		
x. SKIN HYPERPIGMENTATION	☐	☐	☐	☐	☐	☐	☐	☐	☐		
y. STIFF NECK	☐	☐	☐	☐	☐	☐	☐	☐	☐		
z. HEARING LOSS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
aa. BLURRED VISION	☐	☐	☐	☐	☐	☐	☐	☐	☐		
bb. HIGH BLOOD PRESSURE	☐	☐	☐	☐	☐	☐	☐	☐	☐		
cc. NAUSEA/VOMITING	☐	☐	☐	☐	☐	☐	☐	☐	☐		
dd. DIARRHEA	☐	☐	☐	☐	☐	☐	☐	☐	☐		
ee. CONSTIPATION	☐	☐	☐	☐	☐	☐	☐	☐	☐		
ff. BLOODY OR PAINFUL URINATION	☐	☐	☐	☐	☐	☐	☐	☐	☐		
gg. HEPATITIS/JAUNDICE	☐	☐	☐	☐	☐	☐	☐	☐	☐		

	NO	YES: PRIOR TO VIETNAM DUTY	YES: DURING VIETNAM DUTY	YES: AFTER RETURN TO US	YES: NOW	DID YOU SEEK MEDICAL ADVICE? YES	DID YOU SEEK MEDICAL ADVICE? NO	WERE YOU HOSPITALIZED FOR IT? YES	WERE YOU HOSPITALIZED FOR IT? NO	WHAT WAS THE CAUSE?	FOR USAFSAM USE ONLY
hh. HEART PROBLEMS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
ii. KIDNEY PROBLEMS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
jj. NUMBNESS IN HNDS/FT	☐	☐	☐	☐	☐	☐	☐	☐	☐		
kk. EXCESS HAIR GROWTH	☐	☐	☐	☐	☐	☐	☐	☐	☐		
ll. EXCESS HAIR LOSS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
mm. SLEEPLESSNESS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
nn. DIABETES	☐	☐	☐	☐	☐	☐	☐	☐	☐		
oo. CANCER	☐	☐	☐	☐	☐	☐	☐	☐	☐		
pp. STROKE	☐	☐	☐	☐	☐	☐	☐	☐	☐		
qq. IMPAIRED VISION	☐	☐	☐	☐	☐	☐	☐	☐	☐		
rr. DECREASED LIBIDO	☐	☐	☐	☐	☐	☐	☐	☐	☐		
ss. IMPOTENCE	☐	☐	☐	☐	☐	☐	☐	☐	☐		
tt. STERILITY	☐	☐	☐	☐	☐	☐	☐	☐	☐		
uu. INCREASED RESPIRATORY INFECTIONS	☐	☐	☐	☐	☐	☐	☐	☐	☐		

	NO	YES: PRIOR TO VIETNAM DUTY	YES: DURING VIETNAM DUTY	YES: AFTER RETURN TO US	YES: NOW	DID YOU SEEK MEDICAL ADVICE? YES	DID YOU SEEK MEDICAL ADVICE? NO	WERE YOU HOSPITALIZED FOR IT? YES	WERE YOU HOSPITALIZED FOR IT? NO	WHAT WAS THE CAUSE?	FOR USAFSAM USE ONLY
vv. PNEUMONIA	☐	☐	☐	☐	☐	☐	☐	☐	☐		
ww. NOSEBLEEDS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
xx. ABDOMINAL PAIN	☐	☐	☐	☐	☐	☐	☐	☐	☐		
yy. WERE YOU "GROUNDED" FOR MORE THAN 10 DAYS	☐	☐	☐	☐	☐	☐	☐	☐	☐		
14. SMOKING HISTORY											
a. DID/DO YOU EVER SMOKE MARIJUANA?	☐	☐	☐	☐	☐	☐	☐	☐	☐		
b. DID/DO YOU EVER SMOKE CIGARETTES?	☐	☐	☐	☐	☐	☐	☐	☐	☐		

c. HOW MUCH DID YOU SMOKE IN THE PAST

CODES

1	NONE
2	LIGHT (LESS THAN 1 PK/DAY)
3	MODERATE (1-2 PKS/DAY)
4	HEAVY (MORE THAN 2 PKS/DAY)

d. HOW MUCH DO YOU CURRENTLY SMOKE

1
2
3
4

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	NO	YES: PRIOR TO VIETNAM DUTY	YES: DURING VIETNAM DUTY	YES: AFTER RETURN TO US	YES: NOW	DID YOU SEEK MEDICAL ADVICE? YES	DID YOU SEEK MEDICAL ADVICE? NO	WERE YOU HOSPITALIZED FOR IT? YES	WERE YOU HOSPITALIZED FOR IT? NO	WHAT WAS THE CAUSE?	FOR USAFSAM USE ONLY
15. a. DID YOU EVER DRINK ALCOHOLIC BEVERAGES	☐	☐	☐	☐	☐	☐	☐	☐	☐		
16. HAVE YOU EVER TAKEN PRESCRIPTION MEDICATION ON A LONG-TERM BASIS (30 CONTINUOUS DAYS OR LONGER)	☐	☐	☐	☐	☐	☐	☐	☐	☐	NAME OF DRUG	

b. HOW MUCH DID YOU CONSUME IN THE PAST

c. HOW MUCH DO YOU CURRENTLY CONSUME

CODES		
1	NONE	1
2	LIGHT (1-3 DRINKS/WEEK)	2
3	MODERATE (4-7/WEEK)	3
4	HEAVY (8-14/WEEK)	4
5	VERY HEAVY (15+/WEEK)	5

FAMILY HISTORY:

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17. ARE YOU OR WERE YOU EVER MARRIED: YES ☐ NO ☐

a. IF YES, HOW MANY TIMES: ☐☐

18. DATES OF YOUR MARRIAGES:

	YR	MO	REASON FOR SEPARATION					
a.	☐☐	☐☐	DIVORCE/LEGAL SEPARATION	☐	DEATH	☐	N/A	☐
b.	☐☐	☐☐		☐		☐		☐
c.	☐☐	☐☐		☐		☐		☐
d.	☐☐	☐☐		☐		☐		☐

19. HAVE YOU EVER HAD DIFFICULTY FATHERING CHILDREN: YES ☐ NO ☐

20. OF CHILDREN FATHERED, PLEASE SUPPLY THE FOLLOWING INFORMATION (TO THE BEST OF YOUR KNOWLEDGE.)

BIRTH		WAS THIS CHILD PREMATURE			DID THIS CHILD HAVE ANY BIRTH DEFECTS			WHAT IS THIS CHILD'S CURRENT HEALTH STATUS					
YR	MO	YES	NO	UNK	YES	NO	UNK	VERY POOR	POOR	FAIR	GOOD	EXCELLENT	UNK
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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21. HAS YOUR WIFE (WIVES) EVER HAD A MISCARRIAGE: YES ☐ NO ☐ UNK ☐

IF SO, APPROXIMATELY HOW MANY AND WHEN: NUMBER ☐ WHEN (YR) ☐☐

22. HAS YOUR WIFE (WIVES) EVER HAD A STILLBIRTH: YES ☐ NO ☐ UNK ☐

IF SO, HOW MANY AND WHEN: NUMBER ☐ WHEN (YR) ☐☐

23. HAS DOCTOR EVER ADVISED YOUR WIFE(S) NOT TO GET PREGNANT: YES ☐ NO ☐ UNK ☐

IF YES, WHY _____ (ICDA CODE NR) _____

24. IS THERE A HISTORY OF CANCER IN YOUR IMMEDIATE FAMILY:

YES ☐ NO ☐ UNK ☐

		MOTHER	FATHER	GRAND-MOTHER	GRAND-FATHER	BROTHER	SISTER	CODE NR.
TYPE _____	IN	☐	☐	☐	☐	☐	☐	_____
TYPE _____	IN	☐	☐	☐	☐	☐	☐	_____
TYPE _____	IN	☐	☐	☐	☐	☐	☐	_____
TYPE _____	IN	☐	☐	☐	☐	☐	☐	_____

FOR USAFSAM USE ONLY

	MOTHER	FATHER	GRAND-MOTHER	GRAND-FATHER	BROTHER	SISTER	CODE NR.
25. IS THERE A HISTORY OF HEART DISEASE IN YOUR IMMEDIATE FAMILY:							
YES ☐ NO ☐ UNK ☐							
TYPE _____ IN	☐	☐	☐	☐	☐	☐	_____
TYPE _____ IN	☐	☐	☐	☐	☐	☐	_____
TYPE _____ IN	☐	☐	☐	☐	☐	☐	_____
TYPE _____ IN	☐	☐	☐	☐	☐	☐	_____
26. DO YOU KNOW OF ANY SPECIFIC INHERITED DISEASE/CONDITION ON EITHER SIDE OF YOUR OR YOUR WIFE'S FAMILY:							
YES ☐ NO ☐ UNK ☐							
TYPE _____ IN	☐	☐	☐	☐	☐	☐	_____
TYPE _____ IN	☐	☐	☐	☐	☐	☐	_____
TYPE _____ IN	☐	☐	☐	☐	☐	☐	_____
TYPE _____ IN	☐	☐	☐	☐	☐	☐	_____

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27. DO ANY OF YOUR BROTHERS OR SISTERS HAVE CHILDREN WITH CONGENITAL ABNORMALITIES:

YES ☐ NO ☐ UNK ☐

IF YES, SPECIFY TYPE _____ _____

_____ _____

_____ _____

28. DO ANY OF YOUR WIFE'S BROTHERS OR SISTERS HAVE CHILDREN WITH CONGENITAL ABNORMALITIES:

IF YES, SPECIFY TYPE _____ _____

_____ _____

_____ _____

_____ _____

EMPLOYMENT/HOBBIES:

29. WHAT IS YOUR CURRENT JOB: _____ DO YOU REGULARLY COME IN CONTACT WITH

- ☐ ASBESTOS
- ☐ RADIATION
- ☐ HERBICIDES
- ☐ INDUSTRIAL CHEMICALS
- ☐ PESTICIDE
- ☐ OTHER TOXIC CHEMICALS (SPECIFY: _____)

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30. IN OTHER JOBS SINCE YOUR VIETNAM TOUR, DID YOU REGULARLY COME IN CONTACT WITH

- ☐ ASBESTOS
- ☐ RADIATION
- ☐ HERBICIDES
- ☐ INDUSTRIAL CHEMICALS
- ☐ PESTICIDE
- ☐ OTHER TOXIC CHEMICALS (SPECIFY: _____)

31. IN YOUR HOBBIES, DO YOU REGULARLY COME IN CONTACT WITH

- ☐ ASBESTOS
- ☐ RADIATION
- ☐ HERBICIDES
- ☐ INDUSTRIAL CHEMICALS
- ☐ PESTICIDE
- ☐ OTHER TOXIC CHEMICALS (SPECIFY: _____)

32. (SENSATION SEEKING QUESTIONS)

SOUTHEAST ASIA TOUR INFORMATION

33. VIETNAM SERVICE (SOURCE: COMPUTER/INTERVIEW)

TOUR	DATES yr	DATES mo		DATES yr	DATES mo	UNIT OF ASSIGNMENT	AFSC	FLYING TIME
1ST	☐☐	☐☐	to	☐☐	☐☐			
2ND	☐☐	☐☐	to	☐☐	☐☐			
3RD	☐☐	☐☐	to	☐☐	☐☐			
4TH	☐☐	☐☐	to	☐☐	☐☐			
5TH	☐☐	☐☐	to	☐☐	☐☐			
6TH	☐☐	☐☐	to	☐☐	☐☐			
7TH	☐☐	☐☐	to	☐☐	☐☐			

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34. WERE YOU EVER FORCED DOWN IN COMBAT: YES ☐ NO ☐

35. WERE YOU EVER INVOLVED IN A MAJOR AIRCRAFT ACCIDENT: YES ☐ NO ☐

36. WERE YOU EVER WOUNDED IN COMBAT: YES ☐ NO ☐

37. a. IN VIETNAM, WERE YOU EXPOSED TO:

	NO	YES		
		DAILY	MONTHLY	YEARLY
INSECTICIDES	☐	☐	☐	☐
DEFOLIANTS/HERBICIDES	☐	☐	☐	☐
DEGREASING CHEMICALS	☐	☐	☐	☐

38. IF YES TO HERBICIDES, WHICH OF THE FOLLOWING STATEMENTS WOULD BEST DESCRIBE YOUR TYPICAL EXPOSURE:

	ALWAYS	FREQUENTLY	RARELY	NEVER
MY FLIGHT SUIT WAS SATURATED	☐	☐	☐	☐
SEVERAL SPOTS OF THE SUBSTANCE ON MY FLIGHT SUIT	☐	☐	☐	☐
NONE ON MY FLIGHT SUIT, BUT I COULD SMELL IT	☐	☐	☐	☐
NONE ON MY FLIGHT SUIT, I COULD SMELL IT, BUT I COULD SEE THE SPRAY MIST	☐	☐	☐	☐
WAS NOT AWARE OF IT	☐	☐	☐	☐

XIV. Physical Examination Design

A. General Instructions and Cautions to Physicians and Other Examiners

Project Ranch Hand II is a multiyear, multicenter effort to attempt to determine whether or not C-123 aircrew members who were engaged in the aerial spraying of herbicide in Vietnam were exposed to Herbicide Orange constituents sufficient to cause clinical effects. 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 is a cross sectional study of the subject's health at the time of examination. It is of critical importance 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 historical data, laboratory results, ECG, chest x-ray and examination findings will all be brought together for analysis by the study investigators at Brooks Air Force Base, Texas. The examining physician is not, and cannot be expected to arrive at any definitive diagnosis as the full history, laboratory results are not available to him. The obligation for reviewing all results and notifying the subject resides with the study investigators at Brooks Air Force Base, Texas.

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 at the time of the next review of the subject in the prospective phase of Project Ranch Hand. The purpose of these examinations is to establish the health status of the subjects at a point in time, and to establish the presence of findings, if any. Such findings after statistical review of the entire study groups, may permit definition of a chronic residual 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 current review of systems and physical examination. In this role, the examining physician is tasked to collect evidence of the presence or absence of physical signs of abnormality only. Formulation of impressions 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. The examining physician must avoid any expression of opinion regarding the interpretation of

any findings particularly with regards to possible etiology of any findings. The complete history and results of laboratory and procedures will not be available to the examining physician to allow the formulation of a diagnostic impression. If, during the examination, the examining physician discovers evidence of acute serious illness requiring immediate treatment, the normal emergency or urgent care procedures of the facility would apply. If during the examination, the examining physician finds evidence of present illness requiring further medical attention, he should so state to the subject and offer to forward or have forwarded pertinent information to the subject's physician. A clear record of any such advice and tender should be recorded. The ultimate value of the Ranch Hand II Study will lie in 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) On arrival at the examining facility the subject should be briefed on the appointments which have been arranged, the times, and locations.

(2) Collation and forwarding of examination results

A checklist for mailing will be provided. It should be retained by the office primarily responsible (OPR) for the Project Ranch Hand II examination and used to ascertain that all necessary items have been completed and received, or have been directly forwarded by the section performing the examinations. When the OPR for the examinations is ready to forward all materials, the checklist for mailing should be endorsed with the date of mailing as a letter of transmittal and included in the package of material to be mailed to USAFSAM/ES, Brooks AFB TX 78235.

(3) Forms for individual examinations and procedures

The blank forms included for various examinations and procedures may be carried by the patient so as to be available to the examiner or to the lab, or to the department of radiology, etc., as the patient reports for his examinations in those functions. The forms pertaining to the specific function may be withdrawn from the patient's examination package and later returned to the office of primary responsibility.

C. Conduct of the Examination

SECTION	PHYSICAL EXAMINATION	SUBJECT NUMBER

1. GENERAL APPEARANCE

a. ☐ Ectomorph b. ☐ Mesomorph c. ☐ Endomorph d. ☐ Undernourished
e. ☐ Well-nourished f. ☐ Obese g. Appearance (1) ☐ Younger (2) ☐ Same (3) ☐ Older as stated age.
h. Appearance of illness or distress ☐ Yes ☐ No
i. Hair Distribution ☐ Normal ☐ Abnormal ☐ Hirsuitism ☐ Alopecia

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 GROUNDS ☐ NORMAL ☐ ABNORMAL Describe any vascular lesions, hemorrhages, exudates, or papilledema.

☐ A-V nicking ☐ Hemorrhages
☐ ↑ 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 ☐ ☐ Parotid gland enlargement
Enlarged ☐ ☐ R ☐ L
Nodules ☐
Tenderness ☐

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 ☐ S_1 ☐ S_2 ☐ S_3 ☐ S_4

(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.

☐ Heptomegaly ☐ Other mass - Specify:
____ cm Liver Height
☐ 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 attached anatomical figure.

- ☐ Comedones
- ☐ Acneiform lesions
- ☐ Acneiform scars
- ☐ Depigmentation
- ☐ Hyperpigmentation
- ☐ Jaundice
- ☐ Spider angiomata
- ☐ Palmar erythema
- ☐ Petechiae
- ☐ Ecchymoses
- ☐ Lesions Woods Light (UV) Positive

14. MUSCULOSKELETAL ☐ NORMAL ☐ ABNORMAL Describe any abnormality.

- ☐ Muscle - Specify:
  - ☐ Weakness
  - ☐ Tenderness
  - ☐ Abnormal Consistency
  - ☐ Atrophy
- ☐ Spine
  - ☐ Scoliosis
  - ☐ Kyphosis
  - ☐ Tenderness, Level ____
  - ☐ Dec. ROM

Measure and record on attached anatomical figure: Leg Length, Flexed Biceps Circumference of dominant Arm, Thigh & Calf.

- ☐ Pelvic tilt
- ☐ SLR, specify:

15. GENITOURINARY - RECTAL - HERNIA ☐ NORMAL ☐ ABNORMAL

- ☐ Inguinal hernia ☐ R ☐ L
- ☐ Testes

	Absent	Enlarged	Atrophic
☐ R	☐	☐	☐
☐ L	☐	☐	☐

- ☐ Varicocele
- ☐ Epididymis
- ☐ Scotal mass - Specify _____ cm dia
- ☐ Hemorrhoids
- ☐ Prostatic Enlargement
- ☐ Rectal mass
- ☐ Stool Hemoccult Positive

16. LYMPH NODES - CHECK ALL AREAS. ☐ NORMAL ☐ ABNORMAL - SPECIFY CERVICAL, OCCIPITAL, SUPRACLAVICULAR, AXILLARY, EPITRACHLEAR, 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	☐ S4
Sys	☐	☐	☐	☐
Dia	☐	☐	☐	☐

DATE OF EXAMINATION			TYPED OR PRINTED NAME OF EXAMINING PHYSICIAN	RETURN FORM TO:
MONTH	DAY	YEAR		USAFSAM/ ES BROOKS AFB TX 78235
EXAMINING FACILITY			SIGNATURE	

CLINICAL RECORD NEUROLOGICAL EXAMINATION

HEAD AND NECK - Normal to Palpations/Inspection ☐Y ☐N Specify Scar ☐
Asymmetry ☐ Depression ☐
Carotid Bruit ☐No ☐R ☐L
Neck 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-Specify

Associated Movements ☐Arm Swing ☐Normal or Abnormal ☐R ☐L

Muscle Status (strength, tone, volume, tenderness, fibrillations)
Bulk ☐ Normal ☐Abnormal

Tone Upper Extremities ☐Normal or ☐Increased ☐Decreased
☐Right ☐Left

Lower Extremities ☐Normal or ☐Increased ☐Decreased
☐Right ☐Left

Strength - Distal wrist extensors ☐Normal ☐Decreased
Ankle/Toe Dors/Flexors ☐Normal ☐Decreased ☐R ☐L
Proximal Deltoids ☐Normal ☐Decreased ☐R ☐L
Hip Flexors ☐Normal ☐Decreased ☐R ☐L

Abnormal Movements (tremors, tics, choreas, etc.) Fasiculations ☐No ☐Yes (1-4+)
Tenderness ☐No ☐Yes (1-4+)

Tremor ☐No ☐Yes - Specify
Upper Extremity ☐R ☐L } ☐Resting ☐Essential ☐Intention
Lower 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 ☐Both
Heel-Knee-Shin ☐Normal ☐Abnormal ☐Right ☐Left ☐Both
(c) Succession Movements (including check, rebound, posture-holding)
If indicated, check ☐Normal ☐Abnormal ☐R ☐R
Rapidly alternative movements ☐Normal ☐Abnormal ☐R ☐L ☐Both

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

30 AUG 1979

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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 Spurling Maneuver of Neck ☐Normal ☐Abnormal
☐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 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 IV VI Normal ☐ ☐Abnormal - Specify
Pupils-Size (mm) Equal ☐ Unequal ☐ Difference mm____
Shape, position Round ☐ Other ☐ ☐R ☐L
Light, Reaction Normal ☐ Abnormal ☐ ☐R ☐L
Position of Eyeballs

Movements R L

Nystagmus Rotary ☐ Horizontal ☐ Vertical ☐
(Draw position)

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XI

Ptosis R☐ L ☐

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

Sensory R Normal ☐ Abnormal ☐ V_1☐ V_2☐ V_3☐
L Normal ☐ Abnormal ☐ V_1☐ V_2☐ V_3☐

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

SUMMARY OF POSITIVE FINDINGS

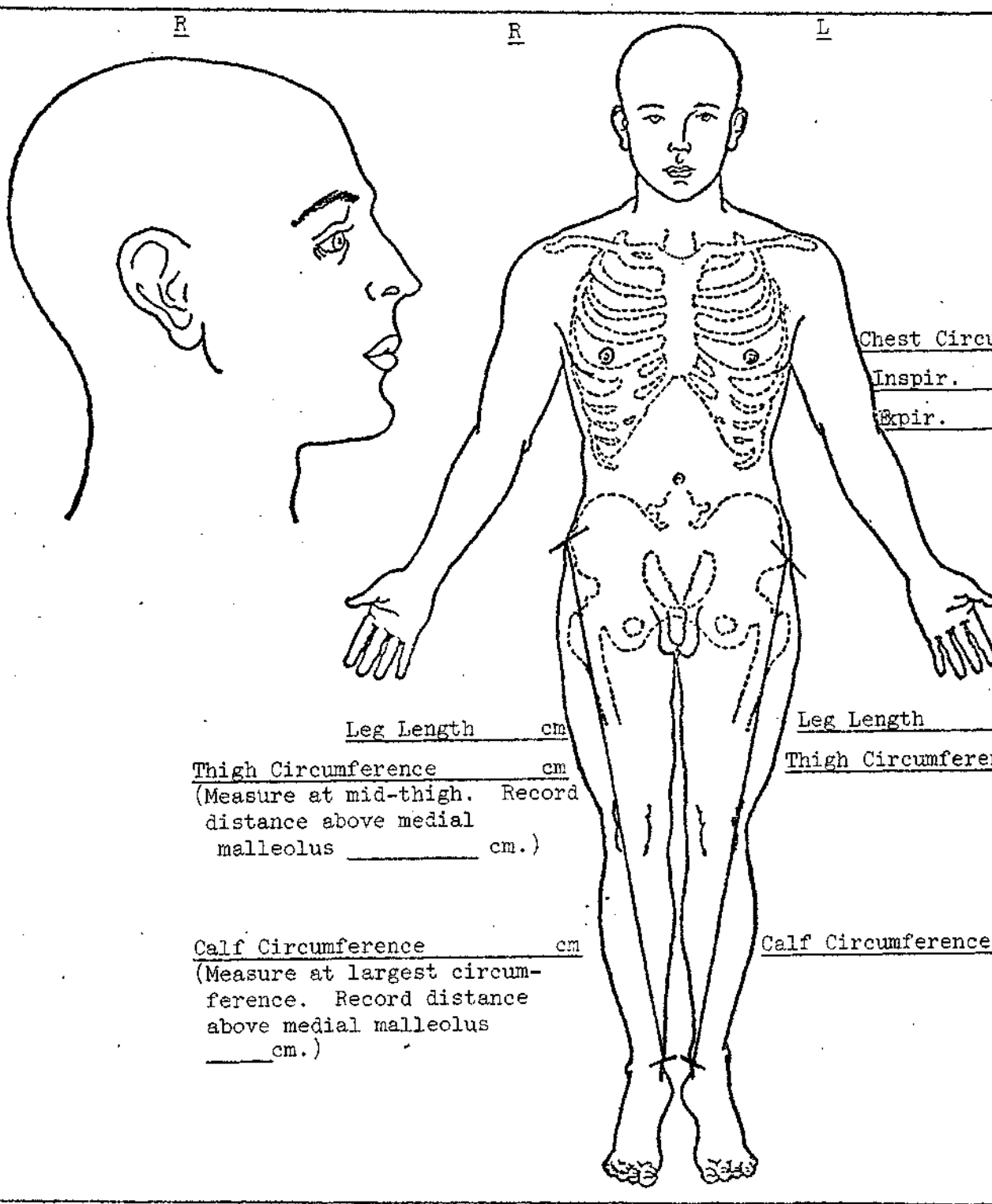
Subjective Objective

Diagnostic Impression

Date Signature

16—61924-8

CLINICAL RECORD	ANATOMICAL FIGURE



Chest Circumference
Inspir. cm
Expir. cm

Leg Length cm

Thigh Circumference cm
(Measure at mid-thigh. Record distance above medial malleolus _____ cm.)

Calf Circumference cm
(Measure at largest circumference. Record distance above medial malleolus _____cm.)

Leg Length cm

Thigh Circumference cm

Calf Circumference cm

PATIENT'S IDENTIFICATION (*For typed or written entries give: Name—last, first, middle; grade; date; hospital or medical facility*)	REGISTER NO.	WARD NO.

ANATOMICAL FIGURE
Standard Form 581
631-104

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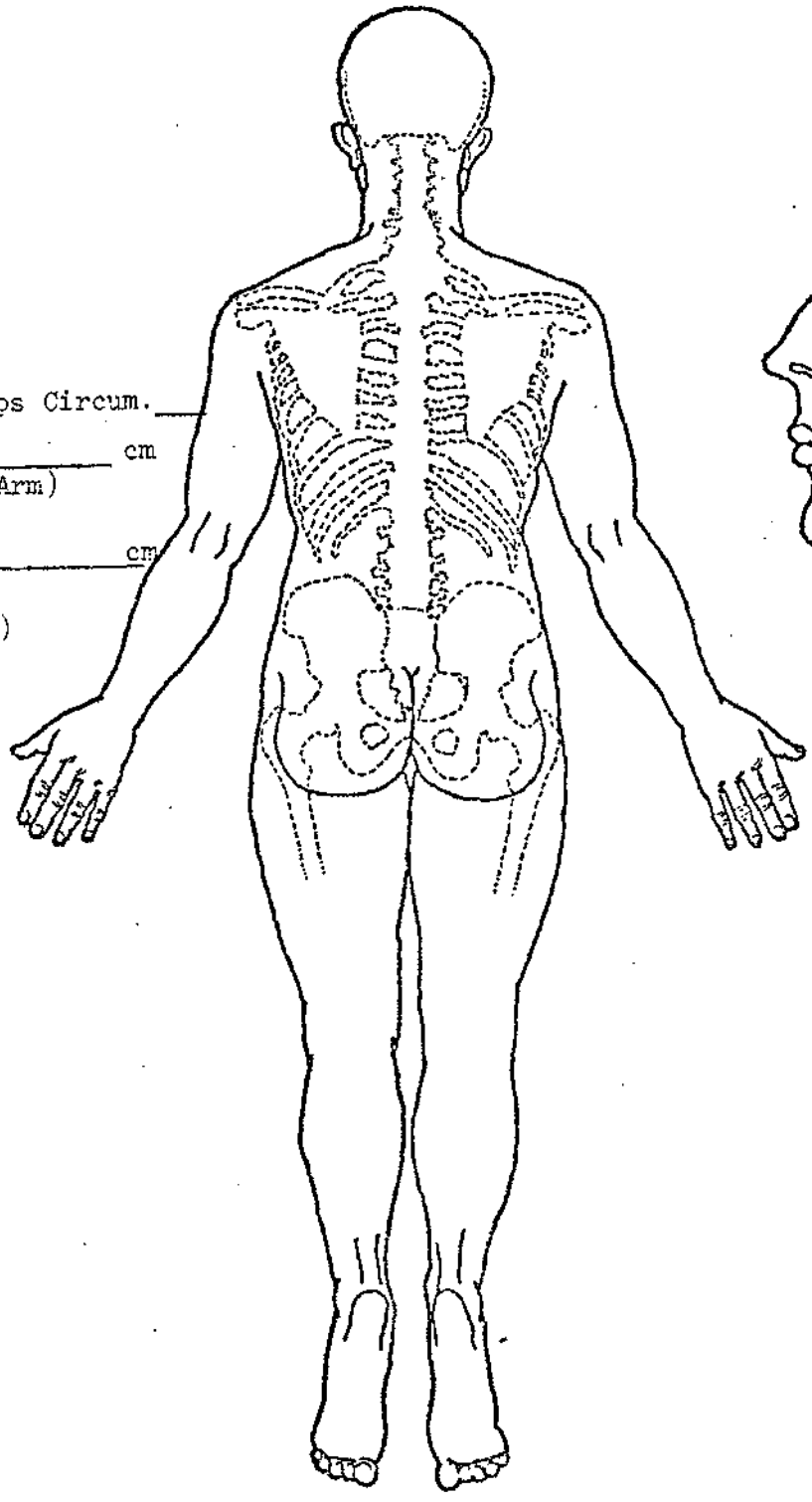
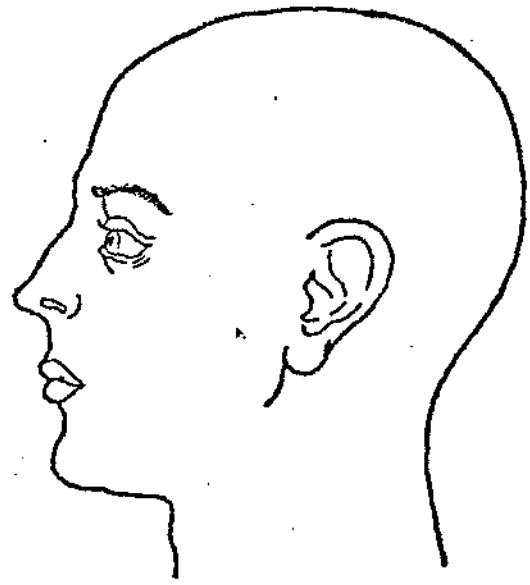
L R L





exed Biceps Circum. _____

_____ cm

Dominant Arm)

ist _____ cm

easure at

Umbilicus)

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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

(1) Accepted published methods are acceptable, e.g., Smorto, Marcio P., and John V. Besmajian; Electrodiagnosis; Harper and Row; NY, 1977.

(2) Standardized temperature is important.

PERONEAL NERVE

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.

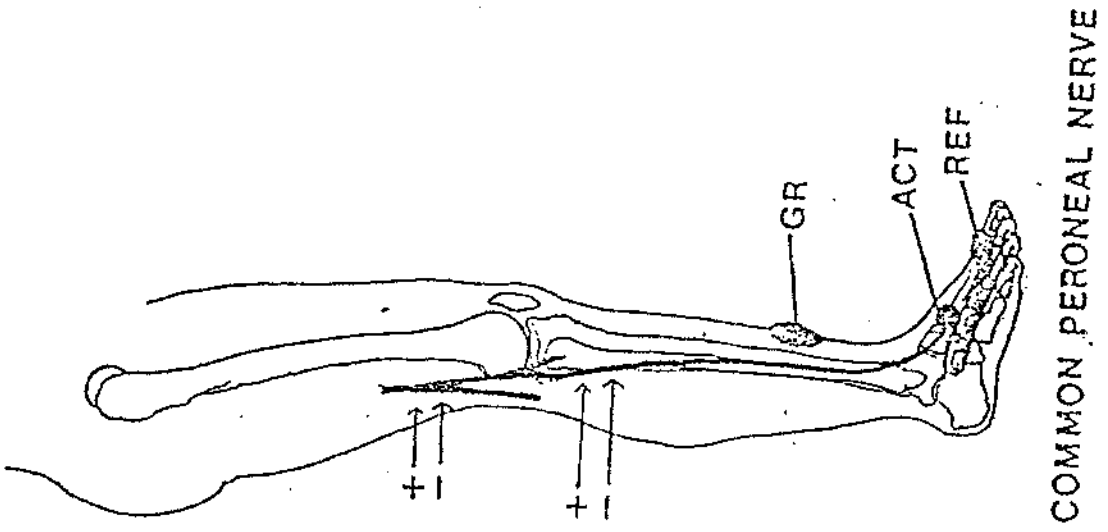
NORMAL VALUES

49.9 ± 5.9 M/sec
Distal latency: 4.5 ± .8 ms

Proximal latencies have been determined for use in BK 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)

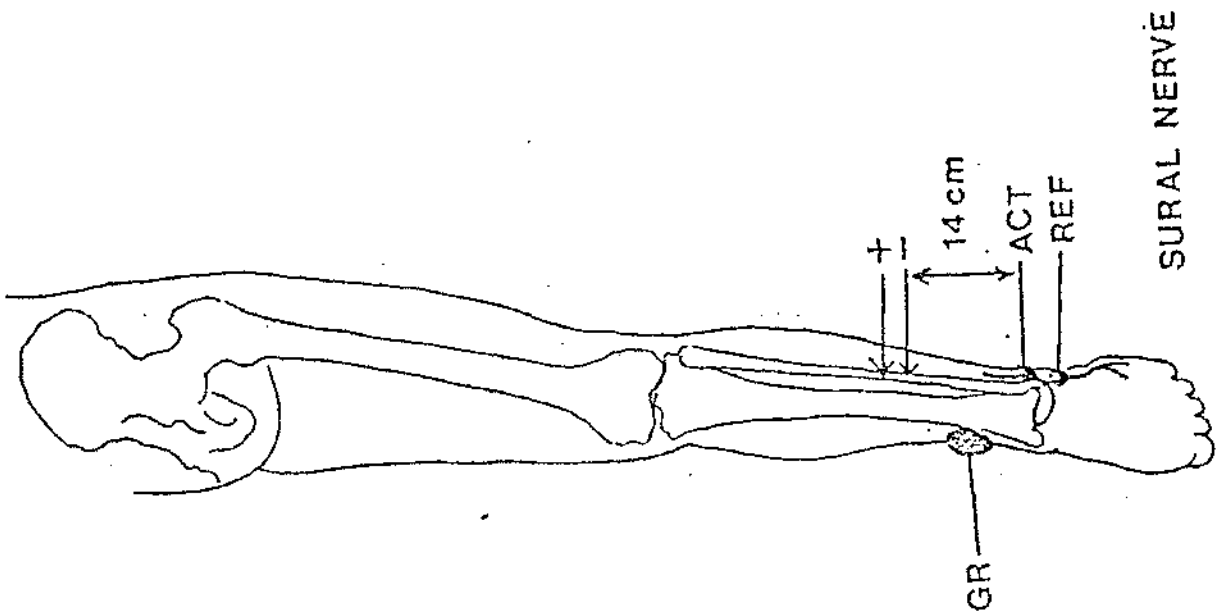


SURAL NERVE

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)

Age	(To Peak)
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

Active electrode is placed over center of abductor digiti quinti; reference over proximal phalanx Dig V. 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 Dig V 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 ± 4.7 M/sec - motor forearm segment
62.7 ± 5.5 M/sec - motor across elbow segment
56.7 ± 4.2 M/sec - sensory orthodromic (to peak)
54.9 ± 3.9 M/sec - sensory antidromic (to peak)

Distal Latency:

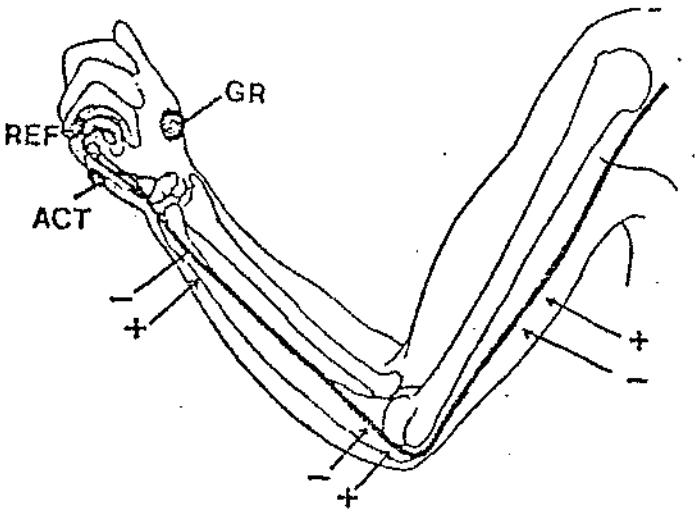
Motor: 3.7 ± .3
Sensory: 3.0 ± .25 Antidromic (peak)
3.0 ± .25 Orthodromic (peak)

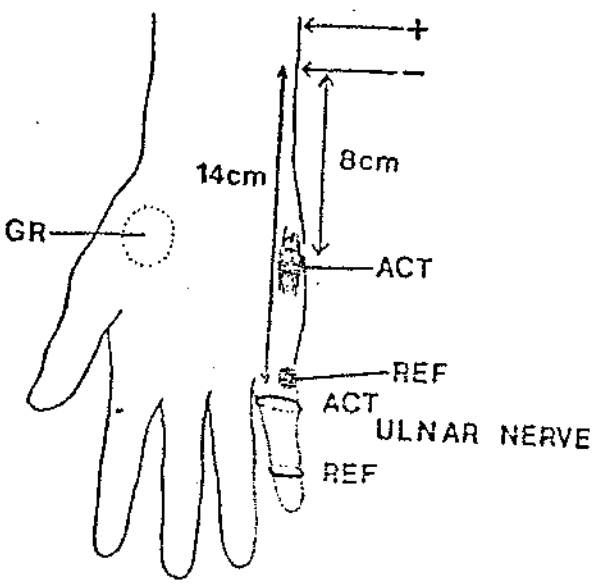
Muscle AP 8-20 mV

Sensory AP 15-50 mV

ADDENDUM

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


GR
REF
ACT
−
+
+
−
−
+


+
−
14cm
8cm
GR
ACT
REF
ACT
ULNAR NERVE
REF

(e) Disposition

Forward the recorded results on the form attached to the examination package to the examining physician.

(2) Psychological Test Battery

(a) General

(1) The battery described elsewhere in the protocol should be available at all major or regional medical centers within the Federal system. All tests yield objective numerical data, and are well-standardized and clinically validated. Since each testing laboratory will probably have only a single Halstead-Reitan apparatus, a maximum of two examinees per eight-hour workday is recommended.

(2) Compared to the general civilian population, characteristic response tendencies are observed on the MMPI and Cornell Index among active duty aircrewmen 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 so as 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 self-administered and standardized neuropsychiatric symptom and complain 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) Shipping Instructions

Forward all test materials as scored with annotations, interpretations, and impressions to the examining physician in your facility or MAIL DIRECTED TO

USAFSAM/ES
BROOKS AFB TX 78235

and provide copy of letter of transmittal to the examining physician.

(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 Brooks AFB.

(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 S 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 Brooks AFB. If applicable, input from the testing technician utilized is encouraged.

(3) 12-Lead Electrocardiogram

(a) A standard 12-lead scalar electrogram is required. If an arrhythmia is observed, a one minute rhythm strip is requested, in addition.

(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 examining physician.

(d) Interpretation:

(1) The electrocardiograms will be interpreted by physicians in the USAF Central ECG Library and compared to previous individual ECG records in the case of rated (pilot or navigator) subjects.

(2) The interpretation and standard Central Library codes will be recorded on SAM Form 222 and forwarded to USAFSAM/ES.

(e) Disposition (USAF Central ECG Library):

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

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

(4) Radiographic Examination

(a) General

The reports of a pneumonitic process in 2,4-D exposure and concern for questions of long-term carcinogenic properties of Herbicide Orange components requires this procedure.

(b) Examination

A standard 14x17 in., standing, teleroentgenogram in the PA position using small nipple markers.

(c) Disposition

Forward the original film to the examining physician or mail to

USAFSAM/ES
Brooks AFB TX 78235

(d) Interpretation

USAFSAM/NGFR will interpret the teleroentgenogram and record the results on SAM Form 23. USAFSAM/NGAR will code the Radiologist's diagnosis (ICDA-9) and forward SAM Form 23 to USAFSAM/ES.

(5) Laboratory

(a) General Instructions for First Day Laboratory Evaluation

(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 non-compliance should be made by the examining physician to aid in the interpretation of the results.

(2) The following is needed:

(a) Blood will be drawn only in the morning into a tube set-up consisting of the following: 4 large 15 ml red top clot tubes and 1 10-ml lavendar top EDTA tube.

(b) Label tubes with patient's full name, Social Security Number, date, and time of drawing.

(c) Perform routine hematology and sedimentation rate on the EDTA tube.

(d) Allow clot tubes to fully clot for at least 30 minutes. Centrifuge and separate hemolysis-free serum into screw-cap polypropylene tubes labeled with the patient's full name, Social Security Number, date, and time of drawing. Also label these tubes with the roman numeral I. Freeze tubes at -20°C as soon as possible (not to exceed 2 hours after drawing).

(e) After the drawing of the fasting specimens, administer 40 gms of glucose per square meter of body surface to the patient. Exactly 2 hours later draw one 7 ml red top clot tube. Alow tube to clot for 30 minutes, centrifuge, and separate hemolysis-free serum into a screw cap polypropylene tube. Label this tube with patient's full name, Social Security Number, date, and time of drawing. Label this tube "Ip.p." Freeze at -20°C as soon as possible not to exceed 2 hours after drawing.

(f) Ship all specimens frozen, packed in dry ice, by Federal Express-Priority one. Submit a patient list containing patient's full name, Social Security Number, and date of drawing. Address to:

USAFSAM/NGP
BLDG 125, Rm W-21
Brooks AFB, TX 78235

WARNING: DO NOT SHIP ON WEEKENDS, THURSDAY OR FRIDAY, OR ON ANY DAY PRIOR TO A FEDERAL HOLIDAY.

(3) The Ranch Hand II Protocol calls for a standard complete blood count, RBC indices, erythrocyte sedimentation rate, and routine urinalysis including a "dip stick" test for porphobilinogen and semen analysis. Since these tests must be done promptly, it is requested that the laboratory of the examining facility draw specimens and accomplish these procedures according to the laboratory's usual routine and forward the results to the examining physician at that facility.

(4) The Ranch Hand II Protocol calls for determination of delta-aminolevulinic acid and products of porphyrin metabolism. For these studies freeze (-20°C) a 100 ml aliquot of urine. The 100 cc urine aliquot must be acidified with 1 ml of glacial acetic acid. Collection of urine should be mid-morning of second day after blood for hormone analysis is drawn. Specific instructions for shipping these specimens will be supplied by USAFSAM/NGP.

(b) General Instructions for Second Day Laboratory Evaluation

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, the following instructions are critical:

(1) Patients should be fasting prior to drawing blood for hormone analysis.

(2) Exact time of each drawing should be recorded on each tube.

(3) One small clot tube (7 ml--without anticoagulant) should be drawn every 20 minutes for one hour. Patients should be kept at rest during the one-hour period. They should not smoke or drink stimulants (coffee or tea).

(4) RBCs should be separated from the serum within 2 hours of drawing the sample and the serum frozen as soon as possible at -20°C in 3 screw-top vials.

(5) Label each of 3 screw-top vials with time, date, and patients name followed by Roman numeral II.

(6) Ship specimens in dry ice in special containers by Federal Express-Priority One. Do not ship on Thursday, Friday, or the day before federal holdiays.

(c) Regional Quality Control of Participating Government Facilities

To insure that hematology and urinalysis results will be comparable from multiple government facilities, it is required that all laboratories participate in the same regional hematology survey. The College of American Pathologists Comprehensive Hematology Survey is strongly recommended. It is also important that participating laboratories run a daily urinalysis control. The USAFSAM Clinical Pathology Laboratory and the USAFSAM Epidemiology Laboratory participate in the College of American Pathologists Comprehensive Hematology Survey and the College of American Pathologists Clincal Chemistry Survey.

(d) Specific Tests

(1) Performed by Local Examining Facility

(a) Hematocrit

(b) Hemoglobin

(c) RBC Indices

(d) While Blood Cell Count

(e) Platelet Count

(f) Erythrocyte Sedimentation Rate

(g) Urinalysis

(h) Semen Analysis (Number, Motility, Morphology)

(2) Performed by USAFSAM/NGP

(a) Blood Urea Nitrogen

(b) Fasting Plasma Glucose

(c) Creatinine

(d) 2-hour Post Prandial Plasma Glucose

(e) Differential Cortisol (0730 and 930 hours)

(f) Cholesterol & HDL cholesterol

(g) Triglycerides

(h) SGOT

(i) SGPT

(j) GGTP

(k) Alkaline Phosphatase

(l) LDH

(m) Serum Protein Electrophoresis

(n) CPK

(o) VDRL

(3) Performed by USAFSAM/EK

(a) LH

(b) FSH

(c) Testosterone

(d) Thyroid Profile (RIA)

(e) Delta-aminolevulinic Acid

(f) Urine Porphyrins

(4) Performed by USAFSAM/EK if liver function studies are abnormal

(a) Anti-nuclear Antibody

(b) Hepatitis Antigens (A and B)

(e) Rationale for Laboratory Tests and RANCH HAND Protocol

(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.

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, weitht 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

(5) Reticuloendothelial system:

(a) White blood cell count

(b) Differential

(c) Serum protein electrophoresis

(6) Hepatic screen:

(a) SGOT

(b) SGPT

(c) GGTP

(d) Alkaline phosphatase

(e) LDH

(f) Cholesterol

(g) HDL cholesterol

(h) Triglyceride

(i) Urine prophyrins

(j) Urine porphobilinogen

(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) The following tests should be peformed only as follow-up for abnormalities in the liver panel:

(a) HAsAG

(b) HBsAG

(c) ANA

(11) Elucidation of sympoms of asthenia:

(a) Testosterone

(b) LH

(c) FSH

E. Forms

PAGE NR.	NERVE CONDUCTION		
SOCIAL SECURITY NUMBER	NAME (*Last, First, MI*)	GRADE	CASE NR.

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.	/ / / / mA	/ / / /

2. Peroneal (one side only) ☐ R ☐ L

		Normal Values for Laboratory
Latency	/ / /./ / ms	/ / /./ /
Distance	/ / / / mm	/ / / /
N.C.V.	/ / /./ / m/s	/ / /./ /
Stm. Curr.	/ / / / mA	/ / / /

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.	/ / / / mA	/ / / /

Ranch Hand II: Psychometric De-Briefing Form

Subject: _____ _____ _____ R L
Name | Test Date | Eval Facility | Handedness

Psychologist/ De-Briefer: _____ _____ _____ _____ Yes No
Name | Title | Degree | Clin/Couns | Cert/Lic

Testing Technician: _____ _____ _____ _____
Same as above | Name | Degree | Test/Experience (Yrs)

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 de-briefing 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_____)

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

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Ranch Hand II: Psychometric De-Briefing Form Continued

Test Score	Valid Results	Reason(s) for Questionably Valid Results	Est of "True" Score/Result
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

PAGE NR.	40 RADIOGRAPHIC DATA

SOCIAL SECURITY NUMBER	NAME *(Last, First, MI)*	GRADE	CASE NUMBER

DATE OF REQUEST			SEX	AGE	ORGANIZATION	REQUESTED BY	X-RAY NUMBER
YEAR	MONTH	DAY					

EXAMINATION REQUESTED

PERTINENT CLINICAL HISTORY

RADIOGRAPHIC REPORT

DATE OF REPORT	SIGNATURE

PAGE NR.	11 ELECTROCARDIOGRAPHIC STUDIES		
SOCIAL SECURITY NUMBER	NAME *(Last, First, MI)*	GRADE	CASE NUMBER

1. DATE OF EXAM		
YEAR	MONTH	DAY

2. TEST RUN NR.	
3. AGE	
4. HEIGHT *(IN)*	
5. WEIGHT *(LBS)*	

6. ROUTINE TRACING		
A. RATE	*(beats/min)*	
B. PR	*(sec)*	
C. QRS	*(sec)*	
D. QT	*(sec)*	
E. MEAN QRS AXIS		
F. WITH TRANSITION AT		
G. MEAN T AXIS		
H. WITH TRANSITION AT		
I. WITH T-WAVES UPRIGHT IN		

J. IMPRESSION

DIAGNOSES *(code)*

1.			4.		
2.			5.		
3.			6.		

7. PRECORDIAL MAP

A. INTERPRETATION

B. COMMENTS

8. MASTER TWO-STEP TEST

A. DATE		
YEAR	MONTH	DAY

B. TEST RUN NR.	
C. FASTING 1-YES 2-NO	
D. 1-SINGLE 2-DOUBLE	

	B.P.		H.R.
BASELINE	SYST	DIAST	
E. 1ST			
F. 2ND			
G. 3RD			
H. POST EXERCISE IMMED.			
I. 2 MIN			
J. 5 MIN			
K. 1. INTERPRETATION			
2. REPOLARIZATION			
3. ARRHYTHMIA			

L. COMMENTS