

**AIR FORCE HEALTH STUDY
(PROJECT RANCH HAND II)**

**AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH
EFFECTS IN AIR FORCE PERSONNEL FOLLOWING
EXPOSURE TO HERBICIDES**

BASELINE MORBIDITY STUDY RESULTS

24 FEBRUARY 1984

Prepared for:
The Surgeon General
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Washington, D.C. 20314

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) In 1979 the United States Air Force (USAF) made the commitment to Congress and to the White House to conduct an epidemiologic study of the possible health effects from chemical exposure in Air Force personnel who conducted aerial herbicide dissemination missions in Vietnam (Operation RANCH HAND). The purpose of this epidemiologic investigation is to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides. This study uses a matched cohort design in a nonconcurrent prospective setting, incorporating mortality, morbidity, and follow-up studies. This		

report presents the results of health information on 2706 Ranch Handers and comparison individuals obtained by questionnaire and 2269 Ranch Handers and comparison individuals undergoing an extensive physical examination.

This baseline report concludes that there is insufficient evidence to support a cause and effect relationship between herbicide exposure and adverse health in the Ranch Hand group at this time. The study has disclosed numerous medical findings, mostly of a minor or undetermined nature, that require detailed follow-up. In full context, the baseline study results should be viewed as reassuring to the Ranch Handers and to their families at this time.

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EXECUTIVE SUMMARY

BASELINE MORBIDITY STUDY

The Ranch Hand II epidemiologic study uses a matched cohort design in a nonconcurrent prospective setting, and incorporates mortality, morbidity, and follow-up studies. The purpose of this report is to present the baseline morbidity study.

The morbidity study design matched each living Ranch Hand (by age, job, and race) to the first living and compliant member of a randomly selected comparison mortality set of 5 individuals, producing a 1:1 contrast. The comparison group was formed from numerous flying organizations which transported cargo to, from, and within Vietnam, but were not involved in aerial spray operations of Herbicide Orange. Of the potential study participants, 99.5% were located. Early in the physical examination phase of the study, it was discovered that 18% of the entire comparison group was ineligible to participate because of inappropriate selection. Thereafter, study eligibility was certified only after a hand-review of personnel records. Next-in-line compliant comparisons entered the study as replacements after fully completing the questionnaire and physical examination. Statistical analyses of these replacement individuals later showed that they differed from the original comparisons in a variety of subtle and often opposite ways. As a conservative measure to avoid possible bias by the inclusion of the replacements in the analyses, a management decision was made to base the statistical tests in this report primarily upon contrasts of the Ranch Hand group to the original comparison group.

The preponderance of data was obtained from the in-home interviews and the physical examination, each conducted under contract to the Air Force by Louis Harris and Associates, Inc., New York NY, and the Kelsey-Seybold Clinic, P.A., Houston TX, respectively. All contacts with the participants were carried out with utmost professionalism and sensitivity. Other morbidity data sources included reviews of medical records, military personnel documents, and birth certificates; in-home questionnaires and telephone questionnaires of the study participant's wives, former wives and, occasionally, their next-of-kin. All aspects of the study were voluntary. As a contract requirement, data collection personnel were blind as to the exposure status of the participants. Ninety-seven percent of the Ranch Handers and 93% of the comparisons participated in the in-home interview. For the physical examination, 87% of the Ranch Handers and 76% of the comparison group participated, a total of 2,272 individuals. This differential attendance at the examination may have introduced a potential participation bias that, in a military population predominantly engaged in flying duties, is multifactorial and complex. All study phases were monitored by stringent quality control standards. Statistical analyses of the data consisted primarily of log-linear models, logistic regression techniques, generalized linear models, matched covariate analyses, and Kolmogorov-Smirnov, chi-square, and t tests.

The physical examination and the in-home questionnaire data were analyzed by major organ system. In terms of general health, more Ranch Handers perceived themselves to be in fair or poor health than did their comparisons. No

group differences were detected for hematocrit or percent body fat determinations. Unadjusted group differences in sedimentation rate were not observed; however, significantly more young comparisons had abnormalities in sedimentation rate than did their Ranch Hand counterparts. There were no statistically significant differences in the occurrence of malignant or benign systemic tumors between the groups. One case of soft tissue sarcoma was found in a comparison member. Significantly more nonmelanotic skin cancer was noted in the Ranch Hand group, but these analyses have not yet considered (adjusted for) sunlight exposure, the prime etiology of these cancers. Such nonmelanotic skin cancer (predominantly basal cell carcinoma) is the most common neoplasm in the White population of the United States. Up to the statistical limits of the study there were no consistent data that showed that the Ranch Handers were developing uncommon cancers, or cancer in unusual sites, or at an unusual age. Measures of fertility and reproductive outcome showed mixed results. It is emphasized that the fertility and reproductive results are preliminary at this time as they are based largely upon subjective self reports that await full medical record and birth certificate verification. Four measures of fertility: number of childless marriages, couples with the desired number of children, the infertility index and the fertility index, showed no difference between the Ranch Hand and comparison groups. A semen specimen obtained from those willing and able to provide one showed no group differences with respect to total sperm count or percent abnormal sperm. There were no significant findings in conception outcomes for miscarriages, stillbirths, induced abortions, or live births. For live birth outcomes no differences were observed for prematurity, learning disability, or infant deaths. There was no significant disparity between groups for the classifications of severe or moderate birth defects. By parental history, however, Ranch Hand offspring showed significantly more minor birth defects (birth marks, etc). Reported neonatal deaths and physical handicaps were also significantly excessive in the Ranch Hand group when contrasted to the total comparison group. All fertility and reproductive findings in the Ranch Hand group showed inconsistent relationships to the herbicide exposure index. Medical records and birth certificates are currently being chronicled for complete verification of all historical findings. A comprehensive neurological examination showed no consistent abnormalities in the cranial nerves, peripheral nerves or central nervous system function of the Ranch Handers. As expected, there was a profound influence of diabetes and alcohol in both groups upon numerous neurological tests. Detailed psychologic data were obtained on all participants at both the in-home interview and the physical examination. It is emphasized that the majority of psychological data was derived from self reported responses during interview and has not been fully assessed for the effect of differential reporting. A variety of subjective deficits (fatigue, anger, fear, anxiety, etc) were significantly more common in the high school educated Ranch Handers. Educational level significantly and consistently influenced most subjective test results. In sharp contrast, more objective performance testing by the Halstead-Reitan battery and IQ testing did not reveal any significant intergroup differences. The roles of overreporting and the Post Vietnam Stress Syndrome in these analyses have not as yet been assessed. Liver function tests and clinical history data showed mixed results. Ranch Handers had some elevated liver enzyme tests and lower cholesterol levels. More Ranch Handers were found to have hepatomegaly and verified histories of prior hepatic disease than their counterpart comparisons. Exposure to alcohol, degreasing chemicals, and industrial chemicals in general, influenced

the liver test results. Ranch Handers reported significantly more symptoms resembling porphyria cutanea tarda than the comparisons, but these data have not been verified by medical record reviews nor were they substantiated by laboratory testing or by physical examination. Exposure index analyses were essentially negative. In the dermatologic evaluation, no cases of chloracne were diagnosed clinically or by biopsy. A thorough questionnaire analysis of acne showed that the incidence, severity, duration, and anatomic location did not differ between groups, and suggested that the historical occurrence of chloracne was highly unlikely in the Ranch Handers. Evaluation of the cardiovascular system showed equal proportions of abnormalities in blood pressures, electrocardiograms, past electrocardiograms, and heart sounds in both groups. Ranch Handers are not having premature heart attacks or generalized heart disease. However, the Ranch Handers showed significant deficits in 2 specific peripheral leg pulses and all leg pulses as a group. These puzzling findings were highly correlated with age and smoking patterns, and verified past heart disease. The assessment of the immune system by laboratory testing was compromised by excessive test variability. An independent review committee determined which test data were suitable for statistical analysis. As an unexpected finding, the test data were significantly influenced by the age and smoking history of the participant; no group differences were detected after adjustment for these factors. A hematologic test battery revealed three red cell abnormalities in the Ranch Hand group, but these were difficult to place into a clinical or epidemiologic context. Evaluation of renal, pulmonary, and endocrine functions generally disclosed small and inconsistent proportions of abnormalities between groups, and were deemed clinically unimportant. An unrefined assessment of all summed and weighted organ system abnormalities by group did not show an aggregation of multisystem disease or malfunction.

Any interpretation of these study data, in whole or in part, must carefully consider the methodical steps required for a proper inference of causality. It is specifically pointed out that many group differences were largely based upon subjective data, and that a subtle effect of differential reporting is suggested but has not been fully evaluated. For objective data, group differences were generally within normal ranges and were not correlated to the herbicide exposure index, nor fell within the expected latency periods following Vietnam service. The proposed clinical end points of dioxin exposure, chloracne, soft tissue sarcoma, and porphyria cutanea tarda, were not found in the Ranch Hand group (study power limitations recognized). Overall, substantial credence is given to the objective study findings, particularly after observing the consistent duplication of the classical effects of risk factors such as age, smoking, alcohol, etc., in almost all clinical areas. Additional work with these baseline data is still required in the areas of data base refinement, statistical testing and bias analysis, exposure index refinement, establishment of the follow-up examination requirements, and collaboration with other dioxin research studies.

This baseline report concludes that there is insufficient evidence to support a cause and effect relationship between herbicide exposure and adverse health in the Ranch Hand group at this time. The study has disclosed numerous medical findings, mostly of a minor or undetermined nature, that require detailed follow-up. In full context, the baseline study results should be viewed as reassuring to the Ranch Handers and their families at this time.

PREFACE

In October 1978, the United States Air Force (USAF) Surgeon General made the commitment to the Congress and to the White House to conduct an epidemiologic study of the possible adverse health effects arising from the herbicide exposure of Air Force personnel who conducted aerial dissemination missions in Vietnam (Operation Ranch Hand). The purpose of this epidemiologic investigation is to determine whether long-term adverse health effects exist, and whether they can be attributed to occupational exposure to herbicides and their contaminants. The study protocol for this effort incorporates a matched cohort design placed in a nonconcurrent prospective setting. The study approach includes mortality, morbidity, and follow-up elements linked tightly in time in order to produce the most data in the shortest time. The study addresses the question: Have there been, are there currently, or will there be any adverse health effects among former Ranch Hand personnel caused by repeated occupational exposure to 2,4,5-Trichlorophenoxyacetic acid (2,4,5,-T) containing herbicides and the contaminant, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)? At the request of the Principal Investigators (see Appendix I) the study protocol was extensively and independently reviewed. The review agencies included: The University of Texas School of Public Health, Houston TX; the USAF Scientific Advisory Board; the Armed Forces Epidemiological Board; and the National Research Council of the National Academy of Sciences. In 1980, the Science Panel of the Agent Orange Working Group was created as an additional peer review agency. This group, redesignated as the Advisory Committee on Special Studies Relating to the Possible Long-Term Health Effects of Phenoxy Herbicides and Contaminants, has consented to the oversight responsibility of the Ranch Hand study and continues to monitor the conduct of this epidemiologic investigation (see Appendix II).

The Air Force Health Study (Ranch Hand II) protocol emphasizes the suboptimal statistical power of the mortality study. The mortality study was motivated by the desire to use a full spectrum epidemiologic approach to the herbicide question. Additionally, the investigators were scientifically obliged to pursue the mortality study because of previous and emerging studies (some with small sample sizes) which suggested the possibility of a soft tissue sarcoma end point (Honchar, 1981; Hardell, 1979; Erikson, 1979). Within the inherent sample size limitation of the Ranch Hand population, detection of such a rare condition will be missed unless there is marked case clustering and correspondingly high relative risks.

Also, because of sample size limitations as well as the myriad of proposed clinical end points, a case-control design was not entertained. In the morbidity phase of the study, the investigators have attempted to enhance statistical power and analytic sensitivity where possible by using (1) precise matching procedures with a replacement strategy to maintain statistical power while averting a loss-to-study bias, (2) exacting quality control procedures, (3) mortality-morbidity linkages, (4) a lengthy follow-up study, (5) state-of-the-art statistical methodology, (6) continuously distributed physical examination variables, and (7) data collection focused on verifiable end points.

The mortality analyses have not revealed any adverse death experience in the herbicide/dioxin exposed cohort. The results of the analyses were consistent: at this time, there is no indication that Ranch Hand personnel have experienced any increased mortality or any unusual patterns of death in time or by cause. They are not dying in increased numbers, at earlier ages, or by unexpected causes.

The fact that only a relatively small number of Ranch Hand deaths were available for analysis is reassuring in itself. However, the fact that adverse effects have not yet been detected does not imply that an effect will not become manifest at a future time or after covariate-adjusted analyses. For this reason, further analyses are intended and mortality in the study population will be ascertained annually for the next 20 years.

The morbidity portion of the study was conducted in two phases; an in-home, face-to-face interview, and a comprehensive physical and psychological examination. Both phases were conducted by civilian organizations under contract to the Air Force, using materials and procedures prescribed by the contract. One thousand, one hundred seventy four (97%) of the Ranch Hand group and 1,156 (93%) of the initially selected comparison group participated in the questionnaire. An additional 376 comparison subjects were interviewed as replacement subjects, bringing the total number of comparison participants to 1,532. Two thousand, seven hundred eight current and former wives of the study participants were interviewed. One thousand forty five (87%) of the Ranch Hand group participated in the physical examination, and 936 (76%) of the initially selected comparison subjects participated. Two hundred eighty-eight replacement subjects also participated in the examination process, giving a total of 2,269 participants, resulting in 1,024 matched pairs for analysis.

The first chapter of this report is devoted to a discussion of the background of the study and the next seven chapters present a summary of the methodology used in gathering, analyzing, and interpreting the data. The results and discussion of these analyses, organized by organ system and/or disease end point, are contained in the remaining chapters.

This report assumes that readers are familiar with statistical and epidemiologic techniques. It also assumes that the reader has a familiarity with the herbicide/dioxin issue and a detailed knowledge of the protocol of the Air Force study, the baseline questionnaire, and the baseline mortality results. In the interest of brevity, the reader is referred to the protocol published as US Air Force School of Aerospace Medicine Technical Report 82-44, the baseline questionnaires published as US Air Force School Aerospace Medicine Technical Report 82-42, and the Baseline Mortality Study Results, 30 June 1983. These reports are available from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161.

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