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

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This report has been reviewed and is approved for publication.



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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		

## 20. ABSTRACT (Continued)

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

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

## PREFACE

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

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

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

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

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

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

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

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

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

## PROTOCOL EVOLUTION

<u>Protocol Version</u>	<u>Date</u>	<u>Major Areas of Change</u>
1	6 June 1979	-----
2	10 July 1979	<ul style="list-style-type: none"> <li>- Expanded discussion of epidemiologic design</li> <li>- Expanded statistical analytic strategy</li> <li>- Consideration of bias sources</li> </ul>
3	30 July 1979	<ul style="list-style-type: none"> <li>- Discussion of exposure index</li> <li>- Development of survival analysis techniques</li> <li>- Expanded discussion of physical examination procedures</li> </ul>
4	30 August 1979	<ul style="list-style-type: none"> <li>- Expanded discussion of exposure concepts</li> <li>- Expansion of mortality study to a 1:3 design</li> <li>- Discussion of compliance factors</li> <li>- Further expansion of physical examination procedures</li> </ul>
5	31 October 1979	<ul style="list-style-type: none"> <li>- Expansion of mortality cohorts to 1:5</li> <li>- Single center examinations</li> <li>- Discussion of the replacement concept for bias correction</li> </ul>
6	28 November 1979	<ul style="list-style-type: none"> <li>- Expanded exposure index discussion</li> <li>- More detailed discussion of statistical analytic strategy</li> </ul>
7	8 October 1980	<ul style="list-style-type: none"> <li>- Increased emphasis on fertility and reproductive endpoints</li> <li>- Enlarged discussion of the mortality analysis</li> <li>- Enlarged discussion of statistical power</li> <li>- Discussion of Quality Control methods</li> </ul>
8	26 November 1980	<ul style="list-style-type: none"> <li>- Presentation of refined data on study population demographic characteristics</li> </ul>

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

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## PROJECT RANCH HAND II

### EXECUTIVE SUMMARY OF THE PROTOCOL

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

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

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

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

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

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

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