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1 INTRODUCTION

This chapter describes the purpose and background of the Air Force Health Study (AFHS), and provides an overview of the study design, morbidity component, and format of this report. In addition, it provides considerations that should be made when interpreting the results provided in this report.

1.1 PURPOSE OF THE REPORT

The subject of this report is the 1997 morbidity follow-up study of the AFHS. The objective of the morbidity follow-up is to continue the investigation of the possible long-term health effects following exposure to herbicides with specific emphasis on Herbicide Orange containing 2,4-D, 2,4,5-T, and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) or dioxin. The principal investigators and the AFHS reports have focused on TCDD. This focus has been the direction for most of the study as derived from the early peer review groups, review of the literature, and the Advisory Committee. However, Model 1, the Ranch Hand versus Comparison contrast, does address in a general way the exposure to picloram and cacodylic acid. In addition, dioxin is a biomarker that the study has used as a surrogate to estimate exposure to phenoxy herbicides, described in greater detail in Section 1.6.2 of this chapter. This report describes the procedures and results of this follow-up study. It was written primarily for epidemiologists, clinicians, and biostatisticians. Familiarity with the Study Protocol and prior mortality and morbidity reports is essential to a full understanding of this 20-year study. This report format has been established to be similar to previous reports so that readers can compare results across study cycles. All statistical analyses in this report were prescribed by the Air Force prior to data collection. This report, prepared by Science Applications International Corporation (SAIC), is submitted as partial fulfillment of Air Force Contract No. F41624-96-C-1012.

1.2 BACKGROUND

In January 1962, President John F. Kennedy approved a program of aerial herbicide dissemination for the purpose of defoliation and crop destruction, in support of tactical military operations in the Republic of Vietnam (RVN). This program, code-named Operation Ranch Hand, dispersed approximately 19 million gallons of herbicides on an estimated 10 to 20 percent of South Vietnam from 1962 to 1971. The herbicides sprayed were code named Herbicide Green, Herbicide Pink, Herbicide Purple, Herbicide Orange, Herbicide White, and Herbicide Blue. 2,4,5-T was an active ingredient in Green, Pink, Purple, and Orange, and TCDD was produced as an inadvertent contaminant of 2,4,5-T during the manufacturing process. 2,4-D was an active ingredient in Purple, Orange, and White. Picloram was an active ingredient in White; cacodylic acid was the active ingredient in Blue. Of the 19 million gallons of herbicide dispersed, approximately 11 million gallons were Herbicide Orange, also called Agent Orange, the primary defoliant of the six herbicides used in the program (1, 2).

From the start, Operation Ranch Hand was heavily scrutinized because of the controversial nature of the program and the political sensitivity to charges of chemical warfare contained in enemy propaganda. The concerns were initially based on military, political, and ecological issues, but shifted to issues of health in 1970. The primary concern in the controversy over the human health effects of these herbicides was related to the dioxin impurity created as a byproduct in the manufacturing process of 2,4,5-T, a component in four of the six herbicides released. The Air Force estimates that 368 pounds of dioxin were released over 6 million acres in South Vietnam (1). Claims of exposure to herbicides, particularly to Herbicide Orange, and perceived adverse health effects among U.S. military service personnel resulted

in substantial controversy and, eventually, a class action litigation. Social concern for the Herbicide Orange issue continues to be reflected in scientific research, media presentations, congressional hearings, and legal action.

Since 1970, governmental agencies, universities, and industrial firms have funded numerous human and animal studies of dioxin effects. A key scientific issue in these studies was the extent of exposure (e.g., who was exposed and to what extent each individual was exposed). Unfortunately, in many of the human studies, population identification and exposure estimation have been scientifically elusive.

In October 1978, the Air Force Deputy Surgeon General made a commitment to Congress and the White House to conduct a health study on the Operation Ranch Hand population. This population comprised the aviators and ground support crews who disseminated the majority of the defoliants in the RVN. The Surgeon General tasked the U.S. Air Force School of Aerospace Medicine at Brooks Air Force Base, Texas, to develop a study protocol. In 1982, after extensive peer review, the epidemiological study began and the Study Protocol was published (3). The Brooks Air Force Base organizations responsible for executing the protocol have been reorganized and renamed several times from 1982 to the present. Currently, the Air Force Research Laboratory, Human Effectiveness Directorate, is responsible for the technical aspects of the study, and the Aeronautical Systems Center, Human Systems Program Office, is responsible for program management.

Studies of serum dioxin levels have suggested that of all the military personnel who served in the RVN, the Ranch Hand cohort was one of the most highly exposed to herbicides. In 1987, when the serum assay became available, the Air Force initiated a collaborative study with the Centers for Disease Control and Prevention (CDC) to measure the serum dioxin levels in the AFHS population. The results of that study demonstrated that substantial elevated levels of dioxin could still be found in the serum of some Ranch Hands (4, 5). If dioxin caused an adverse health effect, then, based on the principle of dose-response, the Ranch Hands should have manifested more or earlier evidence of adverse health.

1.3 STUDY DESIGN

The purpose of the AFHS is to determine whether adverse health effects relative to a similar but unexposed group of Air Force veterans exist and can be attributed to occupational exposure to Herbicide Orange. The study, consisting of mortality, morbidity, and reproductive outcome components, is based on a matched cohort design in a nonconcurrent prospective setting with follow-up studies. A baseline morbidity study and five follow-up morbidity studies over 20 years provide a comprehensive approach to the detection of adverse health effects. Complete details on the design are provided in the Study Protocol.

For the baseline study, the population ascertainment process identified 1,264 Ranch Hand personnel who served in the RVN between 1962 and 1971. At the beginning of the study, a Comparison group was identified consisting of veterans assigned to Air Force units operating C-130 cargo aircraft in Southeast Asia. A computerized selection procedure was used to identify Comparisons with similar characteristics to each Ranch Hand veteran. A maximum of 10 Comparisons for each Ranch Hand was selected, matching on age, race, and military occupation (officer-pilot; officer-navigator; officer-other; enlisted flyer; enlisted groundcrew). After personnel records review, an average of eight Comparison subjects were matched to each Ranch Hand.

A replacement strategy was devised to maintain participation of the Comparisons. Noncompliant Comparisons were to be replaced by Comparisons with the same values of the matching variables (age, race, and military occupation at the baseline examination) and the same health perception. In this way,

the Replacement Comparisons would serve as surrogates for Comparisons who refused to participate. Complete information on the selection and participation of study subjects can be found in Chapter 5, Study Selection and Participation.

The mortality component addresses mortality from the time of the RVN assignment. A baseline mortality study was conducted in 1982, and the mortality follow-up study consists of annual mortality updates for 20 years. For the baseline mortality study and the first four updates, five individuals were randomly selected from the matched Comparison set for each Ranch Hand for a 1:5 design. After 1987, the design was expanded to include all 19,080 veterans in the Comparison population.

1.4 MORBIDITY COMPONENT

The baseline morbidity component, begun in 1982, reconstructed the medical history of each participant by reviewing and coding past medical records. A cross-sectional element, designed to assess the participant's current state of physical and mental health, was based on comprehensive physical examinations and questionnaires. For the morbidity component of the study, each living Ranch Hand and a random living member of his Comparison set were selected to participate in the examination. The morbidity study follow-up comprises sequential questionnaires, medical records review, and physical examinations in 1985, 1987, 1992, 1997, and 2002. Participation was voluntary and each participant signed an informed consent form at the examination site. Previous study results are summarized in each clinical chapter.

The baseline morbidity assessment, conducted in 1982, disclosed few differences between the Ranch Hands and Comparisons (6). The sustained commitment to pursue the Herbicide Orange question to its scientific conclusion was demonstrated by the conduct of the first two morbidity follow-up studies in 1985 and 1987. These examinations provided the opportunity to confirm or refute some of the baseline findings and to explore subtle longitudinal changes. In the follow-up examinations, the physical and mental health status of the participants during the time interval since the baseline study was assessed. The results of the follow-up studies showed a subtle but consistent narrowing of medical differences between the Ranch Hands and Comparisons since the baseline study in 1982. There was not sufficient evidence to implicate a relation between herbicide exposure and adverse health in the Ranch Hand group.

For the baseline study and the 1985 and 1987 follow-up studies, the major focus of the analyses was to compare the health status of the Ranch Hands (i.e., the exposed cohort) with that of the Comparisons (i.e., the unexposed cohort). Methodology to measure dioxin body burden in blood was not made available until February 1987. During the 1987 physical examination, the Air Force initiated a collaborative study with CDC to measure dioxin levels in the serum of Ranch Hands and Comparisons (4, 7, 8). The measurement of serum dioxin levels led to a statistical evaluation to assess dose-response relations between dioxin and the approximately 300 health-related endpoints in 12 clinical areas. This was the first large-scale study of dose-response effects based on a direct measurement of current dioxin. The statistical analyses associated with the serum data evaluated the association between a specified health endpoint and dioxin among the Ranch Hands. The analyses also contrasted the health of various categories of Ranch Hands having differing serum dioxin levels with the health of Comparisons having background levels (10 parts per trillion (ppt) or less) of serum dioxin (9). The analysis of dose-response relations based on serum assays provided an important enhancement from the previous AFHS investigations.

In 1992, the fourth examination was initiated. During a 2½-year period, data for 12 clinical areas were collected and analyzed. As in previous reports, the analysis focused on group differences between the Ranch Hand and Comparison cohorts, as well as on the association of each health-related endpoint with

extrapolated initial and current serum dioxin levels. Findings revealed a consistent relation between dioxin and body fat that was initially noted in the analysis of the 1987 examination results. Cholesterol and the cholesterol-to-HDL ratio were found to be associated with current serum dioxin levels (10). Evidence for a possible association between glucose intolerance, impaired insulin production, and dioxin levels was revealed. Also revealed was a significant association between selected peripheral pulse abnormalities and dioxin levels, and a significant decrement in self-perceived health status of Ranch Hands. Other health endpoints revealed no consistent patterns within or across clinical areas that were suggestive of an adverse relation between health and herbicide or dioxin exposure.

The fifth examination began in 1997. As in 1985, 1987, and 1992, this study was conducted by SAIC in conjunction with Scripps Clinic and National Opinion Research Center (NORC). Analysis of data collected at the 1997 study was the basis for this report. In a departure from previous AFHS reports, dermatologic and renal diseases, other than cancer, were not summarized in this report. Summaries of malignant skin conditions, as well as cancers of the genitourinary system and kidneys, were included in the neoplasia chapter. In past reports, the dermatologic assessment placed primary emphasis on six dermatologic disorders: comedones, acneiform lesions, acneiform scars, inclusion cysts, depigmentation, and hyperpigmentation. Secondary emphasis was given to a composite variable consisting of 16 other minor conditions (generally not associated with chloracne). No significant difference was found for any of these variables in the unadjusted analyses. The adjusted analyses closely mirrored the unadjusted analyses, with no significant difference noted between groups for any variable. Exposure index analyses supported dose-response relations for some of the variables in certain occupational strata, but did not reveal a strong pattern of results suggesting a relation between skin disease and herbicide exposure. In addition, a recently published analysis found no evidence of chloracne in Ranch Hand veterans and no detectable relation between dioxin and acne (11). While a dermatology examination was completed on each participant, because of these results in previous follow-up examinations, a statistical assessment of the data was not performed for the 1997 study.

Medical histories of renal disease and measures of renal function were collected at the 1997 AFHS physical examination; however, assessment of the renal data results was not included in this report for the following four reasons:

1. To our knowledge, there has been no evidence that the kidneys are target organs for dioxin toxicity.
2. The Institute of Medicine report on veterans and Agent Orange did not mention nonmalignant renal disease or renal function as a possible outcome of dioxin exposure (12).
3. No other epidemiological study has documented nonmalignant kidney disease or renal function as a target of dioxin toxicity.
4. All previous statistical analyses of renal disease and renal function have found no association with exposure group or with dioxin level.

Although the dermatology and renal data collected in the 1997 study were not analyzed for this report, they will be combined with the results from the 2002 physical examination and summarized in the final AFHS report.

1.5 ORGANIZATION OF THE REPORT

This report is organized as follows:

- Chapter 1 (Introduction) provides summary background information on the AFHS and discusses specific technical items and issues that may affect the different clinical area assessments.
- Chapter 2 (Dioxin Assay) describes the procedure used to draw blood for the serum dioxin measurements, the analytical method used to determine the dioxin level from the serum, and the quality control (QC) procedures associated with the serum dioxin data.
- Chapter 3 (Questionnaire Methodology) gives an overview of the development and implementation of the participant questionnaires.
- Chapter 4 (Physical Examination Methodology) describes the conduct and content of the physical examinations.
- Chapter 5 (Study Selection and Participation) presents the methods by which participants were selected and scheduled. This chapter also presents a discussion of the participant replacement strategy, the factors known or suspected to influence study participation, and sources of potential bias.
- Chapter 6 (Quality Control) provides an overview of the specific quality assurance and QC measures developed and used throughout the 1997 follow-up study.
- Chapter 7 (Statistical Methods) documents the statistical methods used in the individual clinical area assessments and the statistical procedures and results of the half-life analyses performed by the Air Force.
- Chapter 8 (Covariate Associations with Estimates of Dioxin Exposure) examines the associations between exposure (Ranch Hand, Comparison, and measures of dioxin exposure) and the individual covariates used in the different clinical assessments.
- Chapters 9 through 18 present the results and medical discussions of the statistical analyses of the dependent variables for each clinical area. Each chapter also contains a brief overview of pertinent scientific literature. The 10 clinical chapters are as follows:

  Chapter 9: General Health Assessment
  Chapter 10: Neoplasia Assessment
  Chapter 11: Neurological Assessment
  Chapter 12: Psychological Assessment
  Chapter 13: Gastrointestinal Assessment
  Chapter 14: Cardiovascular Assessment
  Chapter 15: Hematologic Assessment
  Chapter 16: Endocrine Assessment
  Chapter 17: Immunologic Assessment
  Chapter 18: Pulmonary Assessment

- Chapter 19 (Conclusions) summarizes the findings and medical discussions of the 10 clinical areas.
- Chapter 20 (Future Directions) summarizes the anticipated future activities and discusses possible modifications to the existing instruments and methodologies used to investigate the association between health status and dioxin exposure.

1.6 INTERPRETIVE CONSIDERATIONS

In interpreting results from any epidemiological study, no single result should be evaluated in isolation or at face value. Rather, interpretations should be addressed in the context of the overall study design, the data collection procedures, the data analysis methods, dose-response effects, strength of association, temporal relation, biological plausibility, and internal and external consistency. This especially applies to the AFHS. This effort is a large-scale, prospective observational study in which thousands of measurements are generated on each participant. Those measurements and diagnoses are subjected to extensive statistical analyses, testing thousands of individual hypotheses. Each positive result should be scrutinized relative to other findings in this and other studies, and relative to the statistical methods used and the medical and biological plausibility of the results. Conversely, the lack of a positive result only denotes that the hypothesis of no association was not rejected. This has a very different conclusion than the possibly incorrect assertion that there is no effect. In addition, no epidemiological study can establish that there is no effect; i.e., that dioxin is safe (13). Critical considerations in the evaluation of results from this study are reviewed below. Other interpretive considerations, such as adjustments to analyses for known confounders, multiple testing, trends in results within a clinical area, and power limitations, are discussed in greater detail in Chapter 7, Statistical Methods.

1.6.1 Study Design and Modeling Considerations

Biased results will be produced if the assumptions underlying any of the statistical models are violated. Four models were used in this report to analyze the health effects of herbicide exposure in Vietnam. The first model contrasts the exposed population (Ranch Hands) with an unexposed group (Comparisons). The second model evaluates the relation between estimated serum dioxin levels from the time of exposure (i.e., initial dioxin) with each health endpoint. The group contrast model is extended in the third model so that the Ranch Hand group is divided into three categories depending on 1987 levels and estimated initial levels of serum dioxin, and each category is contrasted with the Comparison group. The fourth model evaluates the association between the dependent variables and lipid-adjusted 1987 dioxin levels. The parameters of these four models are summarized in Table 1-1.

As in any epidemiological study, the group contrast (Ranch Hands versus Comparisons) is susceptible to bias toward the null hypothesis of no exposure effect, because of possible exposure misclassification. It may not be true that all Ranch Hands and no Comparisons were occupationally exposed. Recent dioxin data indicate that 44 percent of the Ranch Hands have only background serum dioxin levels. These Ranch Hands either were never exposed or their initially elevated serum dioxin levels may have decreased to background levels during the time period between exposure and serum dioxin measurement. The AFHS has no additional data with which to determine whether Ranch Hands currently having background dioxin levels had elevated levels in the past because there was no method of measuring dioxin in blood prior to 1987, and because no blood was collected and saved prior to 1982.

The model analyzing the association between health endpoints and extrapolated initial dioxin levels (Model 2) also is vulnerable to bias because it directly depends on two unvalidated assumptions: (a) that dioxin elimination is by first-order pharmacokinetics, and (b) that all Ranch Hands have the same dioxin half-life (8.7 years) (14). If dioxin elimination is first-order, but some Ranch Hands have a shorter half-life than others do, then there would have been misclassification of initial dioxin levels.

Table 1-1. Parameters of Exposure Assessment Models

Model	Cohort(s)	Subset of Cohort	Exposure Characterized by:	Covariates in Analysis (not including endpoint-specific covariates)
1	Ranch Hands and Comparisons	All participants	Group (Ranch Hands versus Comparisons and military occupation)	--
2	Ranch Hands	Lipid-adjusted 1987 dioxin measurement >10 ppt	Extrapolated initial dioxin	Body fat at time of blood measurement of dioxin
3	Ranch Hands and Comparisons	RH: 1987 dioxin measurement C: Lipid-adjusted dioxin measurement ≤10 ppt	Group (Ranch Hands versus Comparisons); Ranch Hands categorized according to 1987 dioxin and estimated initial dioxin levels	Body fat at time of blood measurement of dioxin
4	Ranch Hands	1987 dioxin measurement	Lipid-adjusted 1987 dioxin: (102.6*whole-weight 1987 dioxin/total lipids)	--

Note: RH = Ranch Hands.
C = Comparisons.

The half-life of dioxin has been found to change significantly with percent body fat in 213 Ranch Hand veterans with three dioxin measurements, derived from serum drawn in 1982, 1987, and 1992 (14). The half-life increased significantly with higher levels of obesity. The constant 8.7-year half-life used in this report was an estimate derived without adjustment for body fat (14). As a partial solution to the observed relation between half-life and obesity, analyses using dioxin or initial dioxin (Models 2 and 3) were adjusted for percent body fat at the time of the blood measurement of dioxin (see Chapter 7, Statistical Methods). A recent study of dioxin elimination in 20 men exposed during the Seveso accident has validated the first-order model (15), which was the basis for the half-life estimate used in this report; however, validated models of dioxin elimination adjusted for body fat or changes in body fat have not yet been derived.

To account for the possible misclassification of exposure between groups, the third statistical model categorizes Ranch Hands into three levels of exposure: background levels of lipid-adjusted dioxin, and low and high levels of estimated initial dioxin. Each Ranch Hand dioxin category is contrasted with Comparisons having background levels of lipid-adjusted dioxin. Although this model is less dependent upon the accuracy of the initial dioxin estimation procedure than the model using continuous initial dioxin estimates, the classification of the Ranch Hands is subject to bias if the half-life and first-order dioxin elimination assumptions are not true. Also, the Ranch Hands with background levels of lipid-adjusted serum dioxin may contain both unexposed Ranch Hands and exposed Ranch Hands whose serum dioxin levels have decreased to background levels. This will result in a bias toward the null hypothesis of no dioxin effect on the health endpoint.

The model that analyzes the association between a 1987 dioxin measurement and health endpoints (Model 4) may be less subject to bias than Models 1, 2, and 3; however, recent dioxin levels may not be a good measure of exposure if serum dioxin elimination rates differ among individuals. Serum dioxin levels were extrapolated from 1992 measurements to 1987 for Ranch Hand veterans without serum

dioxin levels measured in 1987. Serum dioxin levels also were extrapolated from 1997 measurements to 1987 for Ranch Hand veterans without levels measured in 1987 or 1992. These extrapolations were performed only if the most recent measurement was greater than 10 ppt. Therefore, these 1987 dioxin measurements are subject to bias from a possible violation of the half-life and first-order elimination assumptions that affect the initial dioxin estimates.

1.6.2 The Air Force Exposure Index

In the first three AFHS reports, summarizing results of physical examinations conducted in 1982, 1985, and 1987, the potential relation between health-related endpoints and herbicide exposure in Ranch Hand veterans was assessed using a calculated estimate of herbicide and dioxin exposure. This was called the Air Force exposure index.

The Air Force exposure index was calculated from military records to measure the potential exposure of a Ranch Hand to any of four dioxin-containing herbicides: Herbicides Orange, Purple, Pink, and Green. The index was only an estimate of dioxin exposure because the actual concentration of dioxin in the herbicides varied with type and lot and because exposure varied with individual work habits and duties. The calculation of the index was necessary because direct measures of dioxin exposure were not available at that time. Subsequent to 1987, all outcomes in this study have been assessed versus group contrasts and the dioxin body burden measured in serum. The 1987 results were analyzed twice, first using the Air Force exposure index (10), and then using the dioxin body burden as the measure of exposure (9).

The Air Force exposure index for a Ranch Hand was defined as the product of a dioxin weighting factor and the gallons of dioxin-containing herbicides sprayed during his tour divided by the number of men sharing his duties during his tour. This formula was based on the untested assumption that the exposure of an individual decreased as the number of men available increased. The calculation was performed for each month of his tour, and the monthly results were summed to produce a single exposure index for each Ranch Hand veteran. Each veteran was then assigned to a low, medium, or high exposure category depending on his calculated index and the tertiles of the index for his job category (officer-pilot, officer-navigator, officer-nonflying, enlisted flyer, or enlisted groundcrew). Additional details of the calculation are given in Thomas, et al. (10).

Both measures, the Air Force exposure index and the serum dioxin measurement, have limitations. The exposure index was approximate in that the number of gallons sprayed was based on the totals across all bases rather than at a specific base. In addition, the assumption that exposure decreased as the number of men available increased may not have been reasonable. Interviews with Ranch Hand groundcrew in 1989 revealed that as the workload increased, more men were added to the job, resulting in more men becoming exposed rather than each man becoming less exposed. Finally, the spectrum of behaviors, skills, duties, weather-related work stoppages, work surges due to war conditions, and other factors (some known, some unknown) were not included in the calculation. For example, some Ranch Hand groundcrew had direct contact with bulk quantities of herbicide by filling the tanks and servicing the equipment, while others drove trucks or forklifts away from the flight line. The index did not distinguish between these two kinds of exposure patterns. In addition, some Ranch Hands were assigned to administrative duties, which were indicated in their military records. The Air Force exposure index was defined as zero for those assigned to administrative duties.

The serum dioxin measurement is also limited as a measure of exposure. Although the half-life of dioxin is long (8.7 years), pharmacokinetic studies of Ranch Hand veterans suggest that the half-life varies with body fat (14). Thus, some veterans may eliminate dioxin quickly and others more slowly. Variation of

the dioxin half-life with body fat contributes to variation in the extrapolated initial dose at the time of exposure. In addition, more than 40 percent of Ranch Hand veterans have background levels, precluding extrapolation. Some of those with background levels may have had elevated levels while in Vietnam, while others may not have been occupationally exposed at all. The exposure status of Ranch Hands with background levels cannot be resolved with available data. Furthermore, no validated model exists with which to assess the adequacy of the estimated initial dose as an estimate of actual exposure among those with dioxin levels above background in 1987, 1992, or 1997. Use of serum dioxin measurements as a measure of exposure in Vietnam is further confounded by the other possible sources of dioxin exposure after service in Vietnam. These sources include industrial exposure and environmental factors such as fish consumption and burning of plastics.

The correlation between the Air Force exposure index and serum dioxin levels was described in the dioxin analysis of the 1987 physical examination results (9). These correlations reflected the high percentage of veterans who would be misclassified with regard to dioxin level if the Air Force exposure index was assumed as the standard. For example, 77 of 287 (26.8%) Ranch Hand veterans in the high Air Force exposure index category had dioxin levels less than 9 ppt (see Table 3.5 of reference 9).

Despite these limitations, the serum dioxin level appears to be the most appropriate measure of exposure in this study because of the following:

- It is a direct measurement of the contaminant.
- It has been accurately measured (16).
- It correlates with reported skin exposure to herbicides among enlisted Ranch Hand veterans (17).
- Its elimination in Ranch Hand veterans has followed a plausible pharmacokinetic pattern (14).
- It has been found plausibly associated with health conditions in this study and in other studies (12).

Throughout this report, dioxin levels are used as measures of both exposure to dioxin itself and exposure to dioxin-contaminated herbicides, including Herbicide Orange. Direct contrasts of Ranch Hand and Comparison veterans (Model 1) address the hypothesis of health effects attributable to any herbicide exposure experienced by Ranch Hand veterans during Operation Ranch Hand. Models involving dioxin measurements address the hypothesis that health effects change with the amount of exposure. Dioxin measurements are used as a measure of exposure to dioxin-contaminated herbicides because it is expected that as exposure to such herbicides increased, dioxin levels should increase. Therefore, the dioxin measurement serves as a direct biomarker of exposure to dioxin-contaminated herbicides. No other direct measure or estimate of herbicide exposure is available with which to address hypothetical dose-response relations with health. Some indirect measures, such as self-report of skin contact among enlisted groundcrew, or simply being a Ranch Hand enlisted groundcrew member, are valuable alternatives because dioxin measures suggest that enlisted groundcrew experienced the heaviest exposures. Reported skin exposure is not addressed in this report, but enlisted groundcrew status is addressed in Model 1. The use of dioxin as a measure of exposure to dioxin-contaminated herbicides is consistent with the goal of the study, which is to determine whether health effects exist and can be attributed to occupational exposure to Herbicide Orange (3).

1.6.3 Information Bias

Information bias, represented by the over- or under-reporting of disease symptoms, was minimized by verifying all diseases and conditions with medical records. It is possible that conditions in Ranch Hands may be more verifiable because they may have been seen by physicians more often than Comparisons.

This would be revealed by group differences in the quantity and content of medical records. Because there is no way to quantify these aspects, this potential source of bias remains unexplored. This bias, if it exists, would affect only the models contrasting Ranch Hands and Comparisons (Models 1 and 3) because Comparison data were not used in Models 2 and 4. Information bias due to errors in the data introduced through data entry or machine error is negligible. All laboratory results were subject to strict QC procedures, historical data were verified completely by medical records review, and medical data were subjected to strict QC standards (Chapter 6, Quality Control).

1.6.4 Consistency of Results

All statistically significant findings in this report were subjected to clinical review, ensuring internal consistency throughout the report. In addition, these findings were compared to published results from other studies to ensure external consistency.

1.6.5 Strength of Association

A strong adverse association between exposure and a disease condition, if it exists, would be revealed by an increased relative risk. Some authors have suggested that a statistically significant relative risk greater than 2.0 is cause for concern (18). Statistically significant relative risks less than 2.0 are generally considered to be less important than larger risks because relative risks less than 2.0 can arise more easily because of unrecognized bias or confounding. Relative risks greater than 5.0 are less subject to this concern. The numbers 2.0 and 5.0 are epidemiological guidelines regarding analyses of association between a dichotomous endpoint (disease, no disease) and exposure (yes, no). No such general guidelines have been formulated regarding the analysis of continuously distributed endpoints (such as cholesterol) versus continuously distributed exposure (such as initial or recent serum dioxin measurements).

Statistical power is also an issue in a study of a population this size. A study with a population of 2,121 lacks power to determine increases in relative risks for rare events (such as soft tissue sarcoma) because such events are unlikely to occur in large numbers in a group this small. While certain occupational toxins have a clear diagnostic pathology (e.g., mesothelioma for asbestos, hepatic angiosarcoma for vinyl chloride) virtually nonexistent in the absence of the toxin, other toxins merely increase the risk of nondiagnostic pathology. For example, this study would likely not discern an increase in the relative risk for a rare tumor that does not have a clear diagnostic pathology. By assessing the pathology observed in association with other known environmental risk factors (e.g., tobacco use, alcohol use), it is sometimes possible to provide a limit in the magnitude of effect missed; however, this study has inherent bounds in detecting modest increases in relative risk for infrequent pathology.

1.6.6 Biological Plausibility

The assessment of biological plausibility requires consideration of a biological mechanism relating the exposure and effect of interest. While a lack of biological credibility or even a contradiction of biological knowledge can lead to the dismissal of a significant result, the failure to perceive a mechanism may reflect only ignorance of the state of nature. On the other hand, it is easy to hypothesize biological mechanisms that relate almost any exposure to almost any disease. Thus, while important, the biological explanation of results must be interpreted with caution. In the AFHS, statistically significant results are subjected to medical review and comparison with previously published results in order to identify consistent and biologically plausible results.

1.6.7 Interpretation of Nonsignificant Results

In this study, a lack of significant results relating dioxin to a particular disease only means that the study is unable to detect a relation between dioxin and health. This does not imply that a relation may not exist, but that if it does exist, it was not detected. A lack of significant results does not mean that dioxin is safe or that there is no relation between dioxin and health. The AFHS was not designed to establish safety; rather, this study was designed to determine whether a hazard existed for the exposed personnel. Determination of safety would require a study at least 10 times as large, as determined in a 1985 study presenting minimal sample size criteria for proof of safety and hazard in studies of environmental and occupational exposures (13).

1.6.8 Extrapolation to Armed Forces Ground Troops

Extrapolation of the serum dioxin results to the general population of ground troops who served in Vietnam was difficult because Ranch Hand and ground troop exposure situations were very different. Based on serum dioxin testing results obtained by CDC (8) and others (19), nearly all ground troops tested had current levels of dioxin similar to background levels. Even combat troops who served in herbicide-sprayed areas of Vietnam had current levels similar to those in men who never left the United States (with mean dioxin levels of 4.2 ppt and 4.1 ppt, respectively). The AFHS subgroup most like the ground troops in terms of lipid-adjusted dioxin levels were the Ranch Hands who currently have background levels of dioxin. Therefore, if the results of the AFHS are applied to the general population of other Vietnam veterans, the focus should be on the "Background" Ranch Hand versus Comparison contrast. Extrapolating the results of these analyses to other Vietnam veterans still should be made cautiously, however. There may be demographic distinctions between the "Background" group of Ranch Hands and other Vietnam veterans that may be related to health. Also, if Ranch Hands with background levels of lipid-adjusted serum dioxin showed a significant adverse health effect relative to Comparisons, but if there was no significant effect for Ranch Hands with high serum dioxin levels, the plausibility of such an effect would be questionable, because this would not indicate a dose-response effect. In general, the analyses in this report found that Ranch Hands with background levels of lipid-adjusted dioxin did not show a significant adverse health effect relative to Comparisons.

1.6.9 Considerations for Summarizing Results

A study of this scope with a multitude of endpoints demands, and at the same time defies, meaningful summary tabulation. Such summaries can be misleading because they ignore correlations between the endpoints, correlations between study-examination results, and the nonquantifiable medical importance of each endpoint. In fact, many endpoints are correlated (e.g., psychological scales and indices developed from combining multiple variables). In addition, such tabulations combine endpoints that are not medically or biologically comparable. For example, diminished sense of smell is of less medical importance than the presence of a malignant neoplasm. Nevertheless, the AFHS presents a summary of all statistical results in Appendix G of this report. These summaries, however, can be misleading and must be interpreted carefully—an elementary tally of significant, or nonsignificant, results is not appropriate.

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