AIR FORCE HEALTH STUDY

FINAL REPORT

An Epidemiologic Investigation of
Health Effects in Air Force Personnel
Following Exposure to Herbicides

VOLUME I

1997 Follow-up Examination Results
May 1997 to February 2000

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13. ABSTRACT (Maximum 200 words)

This report summarizes results from the Air Force Health Study (AFHS). The AFHS is an epidemiological study to determine whether adverse health effects attributable to exposure to herbicides exist in veterans of Operation Ranch Hand. Operation Ranch Hand was the unit responsible for the aerial spraying of herbicides, including Herbicide Orange, in Vietnam from 1961 to 1971. A Comparison cohort comprised Air Force veterans who served in Southeast Asia during the same time period that the Ranch Hand unit was active and who were not involved with spraying herbicides. The summarized data were collected during a physical examination administered between May 1997 and April 1998. Of 1,149 eligible Ranch Hands, 870 (75.7%) participated and of 1,761 eligible Comparisons, 1,251 (71.0%) participated. Statistical analyses assessed differences between Ranch Hands and Comparisons and associations between health-related endpoints and extrapolated initial dioxin, dioxin exposure category (Comparisons, background Ranch Hands, low Ranch Hands, high Ranch Hands), and dioxin measured in 1987. The study has insufficient statistical power to assess increases in the risk of rare diseases, such as soft tissue sarcoma. Diabetes and cardiovascular abnormalities represent the most important dioxin-related health problems seen. From a public health perspective, these two areas demand the greatest attention.

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NOTICE

This report presents the results of the 1997 follow-up of the Air Force Health Study, the fifth examination in a series of epidemiological studies to investigate the health effects in Air Force personnel following exposure to herbicides. The results of the 1982 baseline study, the 1985 follow-up study, the 1987 follow-up study, and the 1992 follow-up study were presented in five reports: the Baseline Morbidity Study Results (24 February 1987), the Air Force Health Study First Followup Examination Results (15 July 1987), the Air Force Health Study 1987 Followup Examination Results (16 January 1990), the Air Force Health Study Serum Dioxin Analysis of 1987 Examination Results (7 February 1991), and the Air Force Health Study 1992 Followup Examination Results (2 May 1995).

Given the relationship of the 1997 follow-up to the previous studies, portions of these documents have been reproduced or paraphrased in this report. In addition, portions of the Air Force Health Study Statistical Plan for the 1997 follow-up (20 May 1998) have been used in the development of this report. The purpose of this notice is to acknowledge the authors of these previous study reports and documents.

AIR FORCE HEALTH STUDY

An Epidemiologic Investigation of
Health Effects in Air Force Personnel
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22 February 2000

Volume I

1997 Follow-up Examination Results

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EXECUTIVE SUMMARY

1997 FOLLOW-UP EXAMINATION REPORT

The Air Force Health Study (AFHS) is an epidemiological investigation to determine whether adverse health effects exist in Air Force personnel who served in Operation Ranch Hand units in Vietnam from 1962 to 1971, and whether these adverse health effects can be attributed to occupational exposure to Herbicide Orange (or its dioxin contaminant). A comparison group was formed from Air Force veterans who flew or maintained C-130 aircraft in Southeast Asia (SEA) during the same time period as those who served in the Ranch Hand units and who were not involved with spraying herbicides. The baseline study was conducted in 1982; follow-up studies were performed in 1985, 1987, 1992, and 1997. Participation was voluntary, and consent forms were signed by the participant at the examination site. An additional evaluation is planned for 2002. This report presents the results from the statistical analyses of the data from the 1997 follow-up examination.

In the baseline study, each living Ranch Hand was matched with a randomly selected Comparison based on age, race, and military occupation. At each follow-up study, noncompliant Comparisons were replaced from the set of living Comparisons, matched by age, race, military occupation, and self-perception of health. A total of 2,121 veterans participated in the 1997 follow-up examination. Of the 1,101 eligible Ranch Hands, 870 (79.0%) participated in the 1997 follow-up examination. A total of 839 of the 1,151 eligible Original Comparisons (72.9%) participated. Of the 768 eligible Replacement Comparisons, 412 (53.6%) chose to attend the examination. A total of 1,251 Comparisons attended the 1997 follow-up examination. Eighty-six percent (819 of 949) of living Ranch Hands and 87 percent of living Comparisons (976 of 1,116) who were fully compliant at the baseline examination returned for the 1997 follow-up examination.

This report presents conclusions drawn from the statistical analyses of 266 health-related endpoints in 10 clinical areas: general health, neoplasia, neurology, psychology, gastrointestinal, cardiovascular, hematology, endocrine, immunology, and pulmonary. Analysis was not performed on nine of these endpoints because of a sparse number of abnormalities. Data were collected from a medical records review, previous examinations, and the physical and laboratory examinations and questionnaire administered at the 1997 follow-up examination. The analyses focused on group differences between the exposed (Ranch Hand) and unexposed (Comparison) cohorts, as well as on the association between serum dioxin levels and each health-related endpoint among the Ranch Hands.

Four statistical models were used to evaluate the relation between the health status of study participants and their herbicide or dioxin exposure. The first model (Model 1) examines contrasts between Ranch Hands and Comparisons using group as a proxy for herbicide exposure and does not incorporate serum dioxin measurements. However, it is assumed in this model that all Ranch Hands were exposed and all Comparisons were not exposed to herbicides. Each of the following three models incorporates estimates of serum dioxin in either initial or current form. Current serum dioxin was based on measurements from the 1987 examination. When a 1987 dioxin measurement was not available, measurements from the 1992 or 1997 examinations were used to supplement the 1987 measurement. Initial serum dioxin was extrapolated from the current serum dioxin measurement to time of duty in SEA. The second model (Model 2) examines estimated initial serum dioxin levels, extrapolated from current serum dioxin measurements and assuming first-order kinetics and a constant dioxin elimination rate. The third model (Model 3) categorizes the Ranch Hand cohort according to serum dioxin levels and contrasts each Ranch Hand category with the Comparisons having background serum dioxin levels. The fourth model (Model 4) uses a 1987 lipid-adjusted measure of serum dioxin. This model requires no assumptions about serum dioxin elimination.

The extrapolated initial dose and lipid-adjusted dioxin measurements in Models 2, 3, and 4 may not be good measures of exposure if elimination rates differ among individuals.

In the general health assessment, the self-perception of health analysis revealed significant differences between Ranch Hands and Comparisons, with more Ranch Hands than Comparisons indicating their health as fair or poor. As in previous examinations, the difference was most apparent in enlisted groundcrew, who had the highest average dioxin levels. This observation also was confirmed in the categorized dioxin analysis, where Ranch Hands with the highest dioxin levels perceived their health as fair or poor more often than Comparisons. Also, among Ranch Hands, those with the higher 1987 dioxin levels reported fair or poor health more often than Ranch Hands with lower levels. These results were consistent with the 1985, 1987, and 1992 examinations. No group differences were noted in the appearance of illness or relative age, as recorded by examining physicians, nor were these variables correlated with serum dioxin levels in the Ranch Hand cohort. The analysis of body fat indicated positive associations with dioxin levels. The results of the 1997 examination confirmed those of the 1992 examination and appear consistent with a difference in dioxin pharmacokinetics in obese versus lean individuals. No differences in either the risk of an abnormal erythrocyte sedimentation rate between Ranch Hands and Comparisons or the relations between abnormal erythrocyte sedimentation rates and dioxin levels were observed during the 1997 examination. Erythrocyte sedimentation rates increased as 1987 dioxin levels increased. Longitudinal analyses showed that Ranch Hands, particularly the enlisted personnel, had a greater percentage of abnormal erythrocyte sedimentation rates than did Comparisons during the 15 years of the study since 1982. These analyses also showed that the percentages of abnormalities increased from 1982 to 1997 as dioxin levels increased. This result was seen at the 1987 study, but not in 1992. This positive association raises the possibility of a subtle inflammatory, infectious, or occult malignant disease process related to the body burden of dioxin. In conclusion, fair or poor self-perception of health displayed an adverse association with dioxin. Increased body fat was associated with increased levels of dioxin, a finding most likely related to the pharmacokinetics of dioxin. Longitudinal analyses indicated an increased risk of abnormal erythrocyte sedimentation rates in Ranch Hands over Comparisons in the 15 years of the AFHS, and a relation between abnormal erythrocyte sedimentation rates and levels of dioxin during these 15 years. Other measures of general health revealed no association with levels of dioxin.

In the assessment of malignant neoplastic disease, at the end of 15 years of surveillance, Ranch Hands as a group exhibited a nonsignificant increase in the risk of malignant neoplastic disease relative to Comparisons (relative risk=1.06, 95% confidence interval: [0.80,1.41]). Military occupation contrasts were inconsistent and, therefore, not supportive of an adverse effect of herbicide or dioxin exposure on the occurrence of malignancies. Ranch Hand enlisted groundcrew, the occupation with the highest dioxin levels and, presumably, the highest herbicide exposure, exhibited a decreased prevalence (relative risk=0.78, 95% confidence interval: [0.51,1.19]). Enlisted flyers (relative risk=1.63, 95% confidence interval: [0.91,2.92]) and officers (relative risk=1.14, 95% confidence interval: [0.79,1.65]), occupations with lower dioxin levels, exhibited nonsignificant increases in the prevalence of malignant disease. The risk of malignant disease was nonsignificantly increased among Ranch Hands having the highest dioxin levels (relative risk=1.01, 95% confidence interval: [0.66,1.57]). Longitudinal analyses found no significant group differences with regard to the risk of malignancy and no pattern suggestive of an adverse relation between herbicide or dioxin exposure and the occurrence of malignant neoplastic disease.

In the neurological assessment, four neurological disorders and extensive physical examination data on cranial nerve function, peripheral nerve status, and central nervous system coordination processes were analyzed. Inflammatory diseases, as verified by a medical records review, were increased in Ranch Hands relative to Comparisons in terms of both a group designation and categorized dioxin levels. Peripheral disorders, as verified by a medical records review, increased in Ranch Hands as levels of 1987 dioxin increased. Neck range of motion abnormalities were increased in Ranch Hands relative to Comparisons in

terms of both a group designation and categorized dioxin levels. The increase in abnormalities for Ranch Hands relative to Comparisons was noted in enlisted flyers. An increase in the risk of an abnormal muscle status was observed in Ranch Hand enlisted groundcrew. A significant association between initial dioxin and abnormalities of both visual fields and the patellar reflex was observed. Indices of polyneuropathy showed an increase in the prevalence of abnormality in Ranch Hands relative to Comparisons and a positive association with initial dioxin, categorized dioxin, and 1987 dioxin levels. In summary, although a common etiology in these findings is not apparent, a statistically significant increase in neurological disease appears in Ranch Hands historically, on physical examination, and as reflected in several of the composite polyneuropathy indices. Further, the associations of abnormal neck range of motion with categorized dioxin and a history of peripheral disorders with 1987 dioxin provide evidence of an association of neurological disease with elevated dioxin levels. The results of the analysis of the polyneuropathy indices also provide support of a statistical association between elevated dioxin levels and neurological disease; however, the clinical importance of this finding is uncertain.

Five psychological disorders, which were verified by a medical records review, and 12 measures from the Symptom Checklist-90-Revised (SCL-90-R) inventory were examined in the psychology assessment. The SCL-90-R consisted of nine primary symptom dimensions and three broad indices of psychological distress. In enlisted groundcrew a significantly greater percentage of Ranch Hands than Comparisons had a history of other neuroses. All other significant results from analyses of Ranch Hands versus Comparisons showed a greater percentage of Comparisons than Ranch Hands with high SCL-90-R scores. Associations between initial dioxin and the psychological endpoints were either nonsignificant or revealed a significant decrease in high SCL-90-R scores as initial dioxin increased. Differences in the history of psychological disorders and the prevalence of high SCL-90-R scores were examined between Comparisons and Ranch Hands categorized by dioxin levels. Ranch Hands in the low dioxin category and the low plus high dioxin category displayed a significantly higher occurrence of other neuroses than did Comparisons. The relation between the 1987 dioxin levels and the psychological endpoints was examined and all results were nonsignificant. In summary, Ranch Hand veterans exhibited a significantly increased prevalence of other neuroses among enlisted groundcrew, the military occupation with the highest dioxin levels and, presumably, the greatest herbicide exposure. Consistent increases in the prevalence of other neuroses with dioxin levels were found. No consistent relation was found between any SCL-90-R score and any measure of herbicide or dioxin exposure. The relation between other neuroses and herbicide exposure and dioxin levels will be described in greater detail in a separate report.

The gastrointestinal assessment was based on eight disorders as determined from a review and verification of each participant's medical records, a physical examination determination of hepatomegaly, and 29 laboratory measurements or indices. The laboratory parameters included measurements of hepatic enzyme activity, hepatobiliary function, lipid and carbohydrate indices, and a protein profile. In addition, the presence of hepatitis and fecal occult blood was investigated. Analyses of Ranch Hands versus Comparisons showed higher mean levels of alkaline phosphatase, α-1-antitrypsin, and haptoglobin in Ranch Hands than in Comparisons. In addition, significantly more Ranch Hands than Comparisons had high haptoglobin levels. A review of medical records showed a positive association between initial dioxin and other liver disorders. The other liver disorders condition consisted primarily of nonspecific laboratory test elevations. A significant association between initial dioxin and high levels of aspartate aminotransferase (AST) also was revealed. Analyses of categorized dioxin revealed a significantly higher percentage of other liver disorders among Ranch Hands in the high dioxin category than among Comparisons. Higher mean levels of gamma glutamyl transferase (GGT), triglycerides, and α-1-antitrypsin were observed in Ranch Hands in the high dioxin category than in Comparisons. Ranch Hands in the high dioxin category had a greater prevalence of abnormal AST, triglyceride, and prealbumin levels than did Comparisons. Many significant associations between the laboratory examination variables and 1987 dioxin levels were observed. In both the continuous and discrete forms, the hepatic enzymes alanine

aminotransferase (ALT), AST, and GGT revealed significant, positive associations with 1987 dioxin. In addition, significant positive associations between 1987 dioxin and the ratio of cholesterol to high-density lipoprotein (HDL), triglycerides, and creatine phosphokinase were present. In summary, the analysis of the 1997 follow-up data reflected patterns that have been observed and documented in prior examinations. Isolated group differences exist, but 1987 dioxin levels are strongly related to hepatic enzymes such as AST, ALT, and GGT, and to lipid-related health indices such as cholesterol, HDL, and triglycerides. These results are consistent with a dose-response effect and may be related to unknown subclinical effects of dioxin. Although hepatic enzymes and lipid-related indices showed an association with dioxin, there was no evidence of an increase in overt liver disease.

In the cardiovascular assessment, analyses revealed that Ranch Hands had a significantly higher percentage of participants with a history of heart disease (excluding essential hypertension) than Comparisons and in particular, among enlisted flyers. However, the risk of disease was not significantly increased in Ranch Hand enlisted groundcrew, the military occupation with the highest dioxin levels. The association between heart disease and initial dioxin showed a negative dose-response trend, with heart disease decreasing as initial dioxin increased. Furthermore, Ranch Hands in the background and low dioxin categories had more heart disease than did Comparisons, but this increase was not seen in Ranch Hands in the high dioxin category. Increases in tachycardia and other electrocardiograph (ECG) findings, such as pre-excitation, were seen for Ranch Hands in the high dioxin category, although the analyses were based on a small number of abnormalities. A significant positive association between initial dioxin and evidence of prior myocardial infarction from the ECG was observed in Ranch Hands, and a marginally significant positive association was observed between 1987 dioxin and evidence of prior myocardial infarction from the ECG. A positive association between 1987 dioxin and a history of essential hypertension also was observed in Ranch Hands. In contrast to previous AFHS examinations, no relation was found between peripheral pulse abnormalities and any measure of exposure. In summary the current study has documented that Ranch Hands are more likely than Comparisons to have historical evidence for heart disease (excluding essential hypertension) but are no longer at greater risk for the occurrence of pulse deficits. By all other indices, the prevalence of cardiovascular disease appears similar in both cohorts. For the first time, there is evidence that levels of dioxin may be a risk factor for the development of essential hypertension and prior myocardial infarction as indicated by interpretation of the ECG. As of 1997, the verified history of essential hypertension was associated with 1987 dioxin, and the evidence of prior myocardial infarction from the ECG was associated with initial dioxin. These findings, in conjunction with the increase in the number of deaths caused by diseases of the circulatory system for Ranch Hand nonflying enlisted personnel based on the 1994 AFHS mortality update, showed associations that require further study. A biological mechanism for the relation among dioxin levels and heart disease is unknown.

In the hematologic assessment, five cell count measures, six measures of absolute blood counts, a coagulation measure, and red blood cell morphology were analyzed. In the analyses of these variables, only platelet count exhibited significant dose-response associations with the levels of dioxin. Among enlisted personnel, Ranch Hands exhibited significantly higher mean platelet counts than did Comparisons. Ranch Hands in the high dioxin category also exhibited a significantly higher mean platelet count than did Comparisons. The mean differences were small and, therefore, the clinical importance of these findings is unknown. The results in the 1997 follow-up study parallel the findings of the 1987 and 1992 follow-up studies. In conclusion, apart from platelet count, there appears to be little evidence to support a relation between prior dioxin exposure and hematopoietic toxicity.

The assessment of the endocrine system yielded an extensive evaluation of thyroid, pancreatic, and gonadal function and their relation to dioxin exposure. A significantly increased risk of abnormally high thyroid stimulating hormone values was found in Ranch Hand enlisted groundcrew. A positive association between diabetes and initial and 1987 dioxin was observed. Consistent with previous reports, the prevalence of

diabetes among Ranch Hands with high dioxin levels was significantly increased. A greater percentage of Ranch Hands than Comparisons used insulin to control their type 2 diabetes, primarily among officers and enlisted groundcrew. The percentage of Ranch Hands requiring insulin to control their type 2 diabetes increased with initial dioxin. A greater percentage of Ranch Hands in the high dioxin category required insulin to control their type 2 diabetes than did Comparisons. The percentage of Ranch Hands who treated their diabetes through diet only and the percentage who used oral hypoglycemics increased with 1987 dioxin level. The time to diabetes onset was significantly shorter for Ranch Hands with higher initial dioxin and 1987 levels. Both fasting glucose and α-1-C hemoglobin increased as initial dioxin and 1987 dioxin increased. Increased mean α-1-C hemoglobin levels also were observed for Ranch Hands with high dioxin levels. The presence of fasting urinary glucose also increased with 1987 dioxin. Although cause and effect have not been established, the results cited above provide further evidence for an association between glucose intolerance and levels of dioxin.

The immunologic assessment was based on laboratory data on six lymphocyte cell surface markers, absolute lymphocyte counts, three quantitative immunoglobulins, and six measurements from an autoantibody panel. The six cell marker measurements were carried out on a random sample of approximately 40 percent of the participants because of the complexity of the assay and the expense of the tests. Group analyses revealed significant findings for the analyses of CD16+56+ cell (natural killer cell) counts and for the mouse stomach kidney (MSK) smooth muscle antibody test in enlisted flyers. Among enlisted flyers, the mean CD16+56+ cell count was greater for Comparisons than for Ranch Hands, and a greater percentage of Comparisons than Ranch Hands had a smooth muscle antibody present. Negative smooth muscle and mitochondrial antibody tests are considered to be normal. For these analyses, the magnitude of the mean differences was small and, therefore, the clinical importance of these findings is unknown. Consistent with the previous two physical examinations, IgA increased significantly with initial dioxin, but was not significantly increased in enlisted groundcrew or the high dioxin category, and IgA did not increase significantly with 1987 dioxin. The IgA results, although significant, were small in magnitude and their clinical importance is unknown. When comparing categorized dioxin levels between Ranch Hands and Comparisons, a significantly higher CD16+56+ cell count mean was observed among Comparisons than among Ranch Hands in the high dioxin category. Analyses revealed significant associations between 1987 dioxin levels and CD3+ cell (T cell) count, CD4+ cell (helper T cell) count, and CD3+CD4+ cell (helper T cell) count. The cell counts increased as 1987 dioxin increased. In summary, these findings and the findings from past examinations do not provide evidence of a biologically meaningful dose-response effect for body burden of dioxin on parameters of immunologic assessment. The statistically significant relations suggest the need for continued evaluation.

To assess pulmonary status, verified histories of asthma, bronchitis, and pneumonia were studied. A composite measure of thorax and lung abnormalities, as determined from the presence of asymmetrical expansion, hyperresonance, dullness, wheezes, rales, chronic obstructive pulmonary diseases, or the physician's assessment of abnormality, also was analyzed. A routine chest x ray and five measures of pulmonary function using standard spirometric techniques were analyzed. Few significant increases in adverse pulmonary conditions were observed for Ranch Hands, and isolated and inconsistent associations between the pulmonary endpoints and dioxin were seen. No consistent pattern or dose-response relation was evident. Ranch Hands in the background dioxin category exhibited a significantly higher percentage of abnormalities on the chest x ray than did Comparisons. Ranch Hand officers had a significantly higher prevalence of mild obstructive abnormality than did Comparison officers; the corresponding contrast was not significant in 1992, and officers were not analyzed as a separate stratum in 1982, 1985 or 1987. The relation between mild obstructive abnormality in Ranch Hand officers and other indicators of herbicide exposure, such as job (pilot, navigator, nonflyer), the number of missions flown, the percentage of missions that were herbicide missions, and reported drinking of herbicide (yes, no) will be summarized in a separate report. In summary, analysis of historical, physical examination, and laboratory data revealed no

consistent relation between herbicide exposure or dioxin levels and pulmonary disease. The prevalence of mild obstructive abnormalities was significantly increased in Ranch Hand officers. The meaning of this finding is unclear because the risk was not significantly increased in Ranch Hand enlisted groundcrew—the military occupation with the highest dioxin levels.

Certain facts should be considered when drawing conclusions from the statistical analysis of the 1997 follow-up examination results. First, the Ranch Hand and Comparison veterans were not blinded to group membership. In addition, there are often difficulties associated with multiple testing. With repeated statistical testing, the likelihood of a test indicating some artifactual association is high. But longitudinal comparisons of previous examinations may show a consistent association, supporting a non-artifactual relation. Longitudinal tests, however, of the same population clearly are not independent tests. If a chance association was present at the first physical examination, it would tend to persist in subsequent examinations. Conversely, depending on site and mode of action, the association would be expected to increase with time (if latency or other chronic effects predominate) or decrease with time (if the current dioxin level predominates in the mechanism). It is also important to note that some conditions do not appear with reasonable frequency until middle age or later. Therefore, in the early years of the study an increased relative risk might have been masked by abnormalities too sparse for meaningful analysis.

The report recognizes two major limitations to the study. First, the results cannot be generalized to other groups (such as all Vietnam veterans or Vietnamese civilians) who have been exposed in different ways and to different levels of herbicide. We do not know what effect herbicides or dioxin have at levels other than those found in our study group, or from other sources such as contaminated food. Groups with higher exposures may well have effects not seen in our study. Second, the size of the study makes it difficult to detect increases in rare diseases, so small increases of these diseases may be missed by the study. For example, since liver cancer is very rare, even a tenfold increase may not be detected.

The site and mode of action of dioxin in the body could itself either cause or obscure a relation. Receptors might be activated only after a certain dioxin threshold value had been exceeded—that is, a value exceeding the body's capability to safely store dioxin. If, on the other hand, dioxin caused a competitive inhibition of receptor actions normally stimulated by other substances, there might be a "no-threshold" effect. Depending on the nature (lipid or non-lipid) and type of function of the hypothetical receptor site, an increase in body fat over time might either cause an increase in dioxin effect because of a greater volume of distribution or a decrease in dioxin effect because of a lesser concentration at the receptor site.

Strength of association 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.

A final difficulty is the presence of a true association that is noncausal. An example might be a condition not caused by dioxin, but resulting in or from an altered dioxin half-life. In this case, a correlation might be high in the total absence of causality.

Clearly, there are many issues to be considered in interpreting these results. With these issues in mind, certain assessments were made by looking at a number of factors. Among these factors are longitudinal trends, biological plausibility, consistency with animal toxicology, the presence of a dose-response relation, and strength of association. But, meeting all of these criteria would not guarantee causality, nor would failing these criteria guarantee the lack of an effect. It can be argued, however, that the good faith application of these particular methods should be the starting point for generating hypotheses for experimental examination through in vitro and in vivo testing, as well as through further epidemiological analysis of these and other exposed groups.

Based on the findings of the 1997 examination, and subject to the qualifications considered above, the study investigators have drawn the following conclusions.

1. **Diabetes:** Consistent with previously reported results, current data indicate a significant and potentially meaningful adverse relation between serum dioxin levels and diabetes. A significant dose-response was found, with Ranch Hands in the high dioxin category exhibiting an increase in disease prevalence (relative risk=1.47, 95% confidence interval: [1.00,2.17]). The finding is supported by a dioxin-related increase in disease severity, a decrease in the time from exposure to first diagnosis, and an increase in fasting glucose and α-1-C hemoglobin. Similar patterns were observed in 1987 and 1992.

2. **Cardiovascular Abnormalities:** Cardiovascular findings are mixed, but, in context with the increased cardiovascular mortality in nonflying enlisted Ranch Hands, are suggestive of an adverse effect of herbicide and dioxin exposure. As a group, Ranch Hands have experienced a statistically significant increase in the prevalence of heart disease (excluding essential hypertension) (relative risk=1.26, 95% confidence interval: [1.05,1.51]). The increase was more than doubled among enlisted flyers (relative risk=2.10, 95% confidence interval: [1.27,3.28]), but not significantly increased among enlisted groundcrew (relative risk=1.10, 95% confidence interval: [0.84,1.42])—the military occupation with the highest dioxin levels. The prevalence of diagnosed essential hypertension and the percentage of Ranch Hands with ECG findings of prior myocardial infarction increased significantly with initial dioxin. Peripheral pulse abnormalities increased with dioxin levels in 1987 and 1992, but did not increase with dioxin levels in 1997. These findings, together with increased cardiovascular mortality in Ranch Hand nonflying enlisted personnel, suggest that herbicide or dioxin exposure may be related to cardiovascular abnormalities.

3. **Peripheral Polyneuropathy:** Although a common etiology is not apparent, a statistically significant increase in neurological disease appears in Ranch Hands historically, on physical examination, and as reflected in several of the composite polyneuropathy indices. Peripheral disorders, as verified by a medical records review, increased in Ranch Hands as levels of 1987 dioxin increased. Indices of bilateral peripheral polyneuropathy, confirmed by vibrotactile measurements in the feet, significantly increased with initial dioxin level, were significantly increased in the high dioxin category, and significantly increased with 1987 dioxin. These findings are new and appear consistent with polyneuropathies observed in studies of industrial exposure; however, the numbers of affected veterans are small and the clinical importance of the findings are uncertain.

4. **Serum Lipid Abnormalities:** There were consistent and significant increases in cholesterol, triglycerides, and the cholesterol-HDL ratio with initial and 1987 dioxin. HDL decreased significantly as dioxin increased. These findings also were observed in 1987 and 1992.

5. **Liver Enzymes:** Analysis of liver function reflected patterns that have been observed in prior examinations. Isolated group differences existed, but 1987 dioxin levels were strongly related to increases in hepatic enzymes such as AST, ALT, and GGT and, as previously noted, cholesterol, triglycerides, and HDL. These results were consistent with an adverse dose-response and may be related to subclinical effects of unknown importance. Although hepatic enzymes increased with dioxin, there is no evidence of a corresponding increase in overt liver disease.

6. **Malignant Neoplastic Disease:** At the end of 15 years of surveillance, Ranch Hands as a group exhibited a nonsignificant increase in the risk of malignant neoplastic disease relative to Comparisons (relative risk=1.06, 95% confidence interval: [0.80,1.41]). Military occupation contrasts were inconsistent and, therefore, not supportive of an adverse effect of herbicide or dioxin exposure on the occurrence of malignancies. Ranch Hand enlisted groundcrew, the occupation with the highest dioxin levels and, presumably, the highest herbicide exposure, exhibited a decreased prevalence (relative risk=0.78, 95% confidence interval: [0.51,1.19]). Enlisted flyers (relative risk=1.63, 95% confidence interval: [0.91,2.92]) and officers (relative risk=1.14, 95% confidence interval: [0.79,1.65]), occupations with lower dioxin levels, exhibited nonsignificant increases in the prevalence of malignant disease. The risk of malignant disease was nonsignificantly increased among Ranch Hands having the highest dioxin levels (relative risk=1.01, 95% confidence interval: [0.66,1.57]). Longitudinal analyses found no significant group differences with regard to the risk of malignancy and no pattern suggestive of an adverse relation between herbicide or dioxin exposure and the occurrence of malignant neoplastic disease.

In conclusion, diabetes and cardiovascular abnormalities represent the most important dioxin-related health problems seen in the AFHS. These two areas appear to have the greatest magnitude of effect in terms of quality of life and healthcare costs. Clearly, there are biological interrelations among both of these outcomes that make interpretations difficult. From a public health perspective, these two areas demand the greatest attention.

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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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