

Table of Contents

| | |
|--------------------------------------------|-------------|
| 19 CONCLUSIONS | 19-1 |
| 19.1 INTRODUCTION | 19-1 |
| 19.2 STUDY PERFORMANCE ASPECTS | 19-1 |
| 19.3 STATISTICAL MODELS | 19-1 |
| 19.4 CLINICAL RESULTS | 19-3 |
| 19.4.1 General Health Assessment | 19-3 |
| 19.4.2 Malignant Neoplastic Diseases | 19-4 |
| 19.4.3 Neurological Assessment | 19-4 |
| 19.4.4 Psychological Assessment | 19-4 |
| 19.4.5 Gastrointestinal Assessment | 19-5 |
| 19.4.6 Cardiovascular Assessment | 19-6 |
| 19.4.7 Hematologic Assessment | 19-6 |
| 19.4.8 Endocrine Assessment | 19-7 |
| 19.4.9 Immunologic Assessment | 19-7 |
| 19.4.10 Pulmonary Assessment | 19-8 |
| 19.5 INTERPRETIVE CONSIDERATIONS | 19-8 |
| 19.6 SUMMARY | 19-9 |
| 19.6.1 Diabetes | 19-9 |
| 19.6.2 Cardiovascular Abnormalities | 19-9 |
| 19.6.3 Peripheral Polyneuropathy | 19-10 |
| 19.6.4 Serum Lipid Abnormalities | 19-10 |
| 19.6.5 Liver Enzymes | 19-10 |
| 19.6.6 Malignant Neoplastic Disease | 19-10 |
| 19.7 CONCLUSION | 19-11 |

19 CONCLUSIONS

19.1 INTRODUCTION

This section summarizes the conclusions drawn from the statistical analyses of data from the 1997 follow-up examination of the Air Force Health Study (AFHS). The 1997 follow-up examination was an extension of the baseline, 1985, 1987, and 1992 follow-up examinations. Health endpoints measured at the 1997 examination were analyzed for associations with herbicide exposure and body burden of serum dioxin and were examined longitudinally in relation to data from previous AFHS examinations. A full explanation of the study design and methodology, terminology, and interpretive considerations is provided in Chapters 1 through 8 of this report.

19.2 STUDY PERFORMANCE ASPECTS

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. Participation was voluntary and consent forms were signed by the participant at the examination site. A total of 839 of the 1,151 eligible Original Comparisons (72.9%) participated. Of the 768 Replacement Comparisons eligible for the 1997 follow-up examination, 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.

Although more Comparisons than Ranch Hands refused to participate in the 1997 follow-up examination, there were no significant differences in the reasons for refusal among the two groups. Logistics and health reasons were the most common reasons for refusal, although approximately 25 percent of noncompliant veterans were deemed hostile and a reason for refusal was not determined. Approximately 91 percent of noncompliant Original Comparisons were either replaced or required no replacement (e.g., the Original Comparison was deceased and no Replacement Comparison had been contacted previously).

Ranch Hands reported fair or poor health more often than did Comparisons. This pattern of Ranch Hands reporting poorer health has been observed since the baseline examination. In both groups, veterans who refused were more likely to report fair or poor health than those who were fully compliant. Ranch Hands reported a slightly higher use of medications, but no difference was seen in reported work loss between Ranch Hands and Comparisons.

In summary, the results of these analyses suggested that Ranch Hands may be reporting poorer health than Comparisons and that these group differences are present for both fully compliant participants and refusals. This holds true even after accounting for rank and age differences. In addition, the difference in the percentage of fully compliant participants and refusals reporting fair or poor health was similar for Ranch Hands and Comparisons.

19.3 STATISTICAL MODELS

The analysis of the 1997 follow-up examination results used four statistical models to evaluate the relation between the health status of study participants and their dioxin exposure and serum dioxin levels.

The first model specified contrasts between Ranch Hands and Comparisons using group as a proxy for herbicide exposure and did not incorporate serum dioxin measurements. The remaining three models all incorporated serum dioxin measurements in either 1987 dioxin levels or an estimate of initial exposure based on a first-order extrapolation to the time of tour of duty in Southeast Asia (SEA). The four models are summarized as follows:

- Model 1: Ranch Hands versus Comparisons, for all military occupations (officer, enlisted flyer, enlisted groundcrew) combined and for each military occupation separately
- Model 2: Estimated initial serum dioxin levels using Ranch Hand participants with greater than 10 parts per trillion (ppt) of 1987 lipid-adjusted dioxin
- Model 3: Ranch Hands categorized according to serum dioxin levels versus Comparisons with 10 ppt of 1987 lipid-adjusted dioxin or less
- Model 4: 1987 lipid-adjusted serum dioxin using Ranch Hands only.

In Model 1, the use of group and occupation as a surrogate for herbicide exposure was less subject to the possible biases based on health conditions that may occur with variation in dioxin elimination rates. An implicit underlying assumption was that Ranch Hands were exposed and Comparisons were not exposed to herbicides. Model 2 was based on initial dioxin levels that were extrapolated from lipid-adjusted dioxin measurements above background levels (10 ppt), assuming first-order kinetics and a constant dioxin elimination rate. These lipid-adjusted dioxin measurements were collected primarily at the 1987 examination and supplemented with measurements from the 1992 or 1997 examination when a 1987 measurement was not available. Model 3 was less dependent on the accuracy of the initial dioxin estimation algorithm, but all Ranch Hands with high serum dioxin levels were treated alike without emphasizing the unusually large dioxin doses received by some Ranch Hands. Model 4 was based on lipid-adjusted dioxin measurements and assumed nothing about dioxin elimination other than that Ranch Hands were exposed in Vietnam and their body burdens have decreased over time in an unspecified manner. The extrapolated initial dose and lipid-adjusted dioxin measurements may not be accurate measures of exposure if elimination rates differed among individuals.

Statistical analyses often were applied to clinical endpoints in continuous form (i.e., original measurements) as well as in discrete form (i.e., measurements grouped into categories based on abnormal levels). Analyses also were performed to account for the effects that demographic and personal characteristics (covariates) may have had on the clinical measurements. Such analyses are termed “adjusted analyses.” The relation between health and the measures of exposure in the four models described above are summarized in the next section. The relation between covariates and measures of herbicide or dioxin exposure are described in Chapter 8.

Throughout this report, dioxin levels were 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 levels address the hypothesis that health effects change with the amount of exposure. Dioxin levels were used as a measure of exposure to dioxin-contaminated herbicides because it was expected that as exposure to such herbicides increased, dioxin levels should increase. The dioxin levels, therefore, served as a direct biomarker of exposure to dioxin-contaminated herbicides. No other direct measure or estimate of herbicide exposure is available 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 was not addressed in this report, but enlisted groundcrew status was used in Model 1. The use of dioxin as a surrogate 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.

19.4 CLINICAL RESULTS

This section provides the conclusions from the analyses of the 10 clinical areas—general health, neoplasia, neurology, psychology, gastrointestinal, cardiovascular, hematology, endocrine, immunology, and pulmonary. Tables G-1 through G-24 of Appendix G present the results of the exposure analyses for each of the four models for 257 health endpoints analyzed in the 10 clinical chapters.

19.4.1 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 the percentages of abnormal erythrocyte sedimentation rates between Ranch Hands and Comparisons or 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 two enlisted strata, 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, but the relation with other health conditions is unknown. 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 an abnormal erythrocyte sedimentation rate 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.

19.4.2 Malignant Neoplastic Diseases

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.

19.4.3 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 in the neurological assessment. 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. However, three of the seven Ranch Hand diseases were caused by bacterial infections, suggesting that this finding is unrelated to herbicide or dioxin exposure. 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 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.

19.4.4 Psychological Assessment

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 psychological 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 (adverse) 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.

19.4.5 Gastrointestinal Assessment

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.

19.4.6 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, in contrast to prior examinations, 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.

19.4.7 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.

19.4.8 Endocrine Assessment

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 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 in Ranch Hands as initial dioxin and 1987 dioxin increased. Increased 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 diabetes and levels of dioxin.

19.4.9 Immunologic Assessment

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 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.

19.4.10 Pulmonary Assessment

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.

19.5 INTERPRETIVE CONSIDERATIONS

Certain facts should be considered when drawing conclusions from the statistical analysis of the 1997 follow-up examination results. For example, 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 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.

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.

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 dioxin-exposed groups.

19.6 SUMMARY

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

19.6.1 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.

19.6.2 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.

19.6.3 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, were significantly increased with initial dioxin level, 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 finding is uncertain.

19.6.4 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.

19.6.5 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.

19.6.6 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.

19.7 CONCLUSION

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.