

## CHAPTER 18

### CONCLUSIONS

#### INTRODUCTION

This chapter summarizes the conclusions drawn from statistical analyses performed on approximately 300 health-related endpoints in 12 clinical areas. The analyses focused on dioxin measurements obtained from serum samples collected at the 1987 Air Force Health Study (AFHS) examination. This report summarizes the first large-scale study of dose-response effects based on an accurate measurement of current dioxin levels. This investigation is an important enhancement of the AFHS and supplements previous AFHS reports, which focused on group contrasts between exposed (Ranch Hand) and unexposed (Comparison) cohorts.

Appendix Tables Q-1 to Q-18 summarize the results of the statistical analyses. The significant results discussed in this chapter describe associations between clinical endpoints and dioxin; however, independent of outside criteria (e.g., strength and consistency of association, biological plausibility), they do not necessarily imply cause and effect.

#### Statistical Models

Three statistical models were used to evaluate associations between the health of study participants and their serum dioxin levels:

- Model 1: Estimated initial dioxin levels using Ranch Hand participants only
- Model 2: Current serum dioxin levels and time since military service in Vietnam using Ranch Hand participants only
- Model 3: Four categories of current dioxin levels using both Ranch Hand and Comparison participants.

Analyses based on model 1 depend directly on first-order kinetics and a constant dioxin decay rate, while analyses based on model 2 assume nothing about dioxin elimination other than that Ranch Hands were exposed in Vietnam and that their body burdens have decreased over time in an unspecified manner. Thus, with model 1, one assumes everything is known about dioxin elimination in Ranch Hands; with model 2, one assumes nothing about dioxin elimination in Ranch Hands. All health data were analyzed using both of these models to reduce the likelihood that an effect would be missed due to incorrect assumptions regarding dioxin elimination. Models 1 and 2 were implemented under two assumptions: a minimal assumption and a maximal assumption. The minimal assumption included only Ranch Hands with current dioxin levels above 10 parts per trillion (ppt) (n=521); the maximal assumption expanded the analysis to include all Ranch Hands with current dioxin levels above 5 ppt (n=742). In addition, model 3, using both Ranch Hands and Comparisons, assessed the health consequences of current dioxin body burdens above background. This assessment required no assumptions about when or how increased dioxin body burdens were attained.

Statistical analyses often were applied to clinical endpoints in continuous (i.e., original measurement) and discrete (i.e., measurements grouped into categories based on abnormal levels) forms. Analyses also were performed to account for the effects that demographic and personal characteristics may have had on the clinical measurements. Such analyses are termed "adjusted analyses."

## **RESULTS**

### **General Health Assessment**

The general health assessment examined the associations between serum dioxin levels and the following five variables: self-perception of health, appearance of illness or distress at physical examination, relative age, percent body fat, and erythrocyte sedimentation rate. These variables were thought to be sensitive to the overall state of health rather than to any single organ system. Of these variables, the percent body fat and sedimentation rate consistently showed significant positive associations with the initial and current levels of dioxin.

Percent body fat can serve as an indicator of the presence of subclinical disease. For these analyses, percent body fat was determined from a formula using weight and height. The findings for percent body fat are consistent with the association between dioxin and diabetes mellitus in the endocrine assessment and lipids in the gastrointestinal assessment.

Sedimentation rate can be a sensitive, although nonspecific, index of general health. Consistent with the findings in this report, the Ranch Hand group had a significantly higher mean sedimentation rate than the Comparison group in both the previous report of the 1987 examination and the 1985 examination report. The results from these reports suggest that a subtle, chronic inflammatory response may be related to higher levels of dioxin exposure. The association between diabetes and dioxin noted in the endocrine assessment might be responsible for the sedimentation rate findings. However, a significant positive association between dioxin and sedimentation rate remained when the analysis was restricted to nondiabetics. As expected, diabetics had higher sedimentation rates than nondiabetics.

The longitudinal analyses of self-perception of health demonstrated significant positive associations with initial dioxin and current dioxin. However, the percentage of participants who reported fair or poor health decreased by more than 50 percent from 1982 to 1987. In the longitudinal analyses of sedimentation rate, the percentages of abnormalities in 1987 differed significantly among the current dioxin categories, with Ranch Hands in the low and high current dioxin categories exhibiting significant positive relative risks in relation to the background current dioxin category.

### **Malignancy Assessment**

The relationship between dioxin and malignant and benign neoplasms, carcinomas in situ, and neoplasms of uncertain behavior or unspecified nature was assessed. Neoplasm refers to any new growth that may or may not be malignant; malignant neoplasms are neoplasms capable of invasion and metastasis. The evaluation was based on the incidence of neoplasms after the Southeast Asia (SEA) tours. Skin and systemic neoplasms were studied separately. The malignant skin neoplasm analyses were based on non-Blacks only;

the benign skin neoplasms analyses included Blacks. Risk factors such as age, ability to tan, cumulative sun exposure, and parental ethnicity, as well as eye, skin, and hair color, were considered as candidate covariates in the analyses of skin neoplasms.

The results of the serum dioxin analyses for the skin neoplasm assessment did not support a positive dose-response relationship. In each of the three previous AFHS reports, an increased risk of basal cell carcinomas was noted in the Ranch Hand group relative to the Comparison group. According to the group contrasts for the 1985 and 1987 examinations, Ranch Hands also had a significantly increased risk of sun exposure-related skin neoplasms (predominantly basal cell carcinoma, but also squamous cell carcinoma, melanoma, and malignant epithelial neoplasms not otherwise specified).

In this report, the initial dioxin analyses and the current dioxin and time since tour analyses found that the relative risks for basal cell carcinoma and sun exposure-related skin neoplasms often were less than 1. The relative risk was significantly less than 1 for the adjusted model 1 analyses of basal cell carcinoma on the ear, face, head, and neck under the minimal assumption. There was no increased risk for the development of any skin neoplasm related to dioxin except for occupation-specific analyses.

Analyses were performed within military occupational groups (officer, enlisted flyer, and enlisted groundcrew). Statistically significant increases in the incidence of basal cell carcinoma of sites other than the ear, face, head, or neck were found for the associations with the initial and current serum dioxin levels for Ranch Hand enlisted flyers. However, these results may be the result of a multiple-testing artifact, since they were not noted for the Ranch Hand enlisted groundcrew who, as a group, had higher levels of serum dioxin than the enlisted flyers. The Air Force will continue to monitor basal cell carcinoma in subsequent phases of the study.

The serum dioxin analyses detected significantly increased risks of benign, but not malignant, systemic neoplasms. Under the maximal assumption, Ranch Hand participants with high levels of initial dioxin had a greater incidence of benign systemic neoplasms (9.7%) than did Ranch Hands with medium (5.7%) or low (1.6%) levels (approximately 75% of benign neoplasms in Ranch Hands and 70% in Comparisons were lipomas). Under both assumptions, the adjusted current dioxin and time since tour analyses revealed that current dioxin was associated with significantly increased risks of benign systemic neoplasms for Ranch Hands with earlier tours. In the categorized current dioxin analyses, the adjusted relative risk was 2.13 for Ranch Hands in the high current dioxin category (>33.3 ppt).

By contrast, the adjusted initial dioxin analyses found that the relative risks were less than 1, but not significant, for malignant systemic neoplasms. The model 3 analyses showed that Ranch Hands in the low current dioxin category (>15-33.3 ppt) had a significantly increased risk relative to Comparisons in the background category (10 ppt or less), but none of the Ranch Hands in the high current dioxin category had any malignant systemic neoplasms.

At the 1985 examination, one Ranch Hand and one Comparison had verified soft tissue sarcoma (STS) (fibrous histiocytoma and fibrosarcoma, respectively). The Ranch Hand was

not part of the 1987 study because he died prior to his scheduled examination; the Comparison with the fibrosarcoma participated in the 1987 examination. At the 1985 examination, one Ranch Hand was classified as having a suspected leukemia, Hodgkin's disease (HD), or non-Hodgkin's lymphoma (NHL). He was subsequently diagnosed as having leukemia by the time of the 1987 examination. There was one verified case of NHL in a Ranch Hand at the 1987 examination.

In summary, dioxin was significantly associated with an increased risk of benign, but not malignant, systemic neoplasms. The study provided no evidence of increased risk for the neoplasms most commonly thought to be linked with exposure to chlorophenols (HD, NHL, and STS). However, the number of participants with these specific neoplasms was very small, limiting the statistical power to detect a significant relative risk. The increased incidence of basal cell skin neoplasms in Ranch Hands documented in previous examination cycles was not associated positively with serum dioxin, except among the enlisted flyers with basal cell carcinomas at sites other than the ear, face, head, or neck.

### Neurological Assessment

The neurological assessment was based primarily on extensive physical examination data on cranial nerve function (CNF), peripheral nerve status, and central nervous system (CNS) coordination processes. These data were supplemented by verified histories of neurological diseases.

The neurological analyses revealed no consistent evidence to indicate that dioxin was associated with neurological disease. The analyses of hereditary and degenerative diseases found no association with dioxin, in contrast to the finding from the previous report that showed a significant increase in benign essential tremor in Ranch Hands. The adjusted analyses for the other historical variables also were not significant.

There were few statistically significant associations between dioxin and the physical examination variables. The power to detect significant results was limited for many of the CNF and CNS variables because there were few abnormalities. Peripheral neuropathy clearly has been shown to be associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure in other studies, but no significant findings were noted for the eight peripheral motor and sensory indices.

Most of the significant findings in the neurological assessment were noted for the CNS variables. For the adjusted model 3 analyses, there was a significantly increased risk of coordination abnormalities for Ranch Hands in the high current dioxin category relative to Comparisons in the background current dioxin category. This finding is consistent with the previous report, which found that Ranch Hands on the whole had significantly more coordination abnormalities than Comparisons. The adjusted model 3 results for the CNS index (a composite variable based on coordination, tremor, and gait) displayed similar findings. The adjusted model 1 results were marginally significant for coordination and significant for the CNS index. The longitudinal analyses of the CNS index under the maximal assumption revealed a marginally significant positive association with initial dioxin.

In summary, dioxin was associated significantly with coordination and the CNS index, but CNF and peripheral nerve status variables were not associated with dioxin.

### **Psychological Assessment**

The psychological assessment examined verified psychological disorders, reported sleep disorders, and the results of two clinical psychological tests: the Symptom Check List-90-Revised (SCL-90-R) and the Millon Clinical Multiaxial Inventory (MCMI). The SCL-90-R is a 90-item checklist of physical and mental symptoms that provides a reasonable measure of health-related concerns and associated anxiety, depression, and general emotional discomfort. The MCMI provides backup measures of depression, anxiety, somatization, and hypochondriasis for the SCL-90-R, while also screening for personality patterns, disorders, and major psychiatric syndromes, including psychoses. Both the SCL-90-R and the MCMI have been used extensively in research and in some clinical settings requiring economical assessment of psychiatric disorders, physical disability status, and response to specific therapies. The SCL-90-R variables were discretized as abnormal or normal for analysis, while each MCMI variable was analyzed in its continuous form.

The serum dioxin analyses did not indicate that dioxin was associated significantly with either the verified questionnaire disorders or the reported sleep disorders. The unadjusted analyses for the SCL-90-R variables were often significant, but in most cases became nonsignificant after covariate adjustment. This was due primarily to adjustment for education. The education covariate was associated indirectly with serum dioxin levels because both of these variables were highly associated with military occupation and rank.

By contrast, the adjusted analyses for many of the MCMI variables showed a significant association with dioxin. After adjustment, the initial dioxin analyses found that 9 of the 20 MCMI scale results were significant under either the minimal or maximal assumption (positive: schizoid, avoidant, dependent, schizotypal, somatoform, psychotic thinking, and psychotic depression scores; negative: histrionic and narcissistic scores). Most of these variables also were associated significantly with current dioxin levels in the model 2 analyses based on Ranch Hands with more than 18.6 years since service in SEA. The adjusted model 3 analyses detected fewer significant results. Ranch Hands in the high current dioxin category relative to Comparisons in the background current dioxin category had significantly higher mean schizoid and schizotypal scores and a significantly lower mean histrionic score.

Although the MCMI results suggest the possibility of a relationship between dioxin and personality disturbances and/or psychotic disorders, they are inconsistent with the results for the verified questionnaire data and the SCL-90-R scales. The relatively large number of statistically significant MCMI results may be explained in part by substantial overlap inherent to the construction of test scales. Because there was a lack of consistency across similar variables included in the SCL-90-R, MCMI, and verified disorders, the available evidence does not suggest that the body burden of dioxin is related to psychological or psychophysiological disorders.

## **Gastrointestinal Assessment**

The gastrointestinal assessment examined the history of eight categories of liver disease: viral hepatitis, acute and subacute necrosis of the liver, chronic liver disease and cirrhosis (alcohol-related and nonalcohol-related were analyzed separately), liver abscess and sequelae of chronic liver disease, other disorders of the liver (abnormal liver scans, abnormal enzyme elevations, unspecified hepatitis, and unspecified disorders of the liver), hepatomegaly, and jaundice. Verified histories of ulcers and skin patches, bruises, and sensitivity also were analyzed. Hepatomegaly diagnosed at the physical examination was investigated in addition to 13 laboratory variables (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transpeptidase [GGT], alkaline phosphatase, d-glucaric acid, total bilirubin, direct bilirubin, lactic dehydrogenase, cholesterol, high-density lipoprotein [HDL], the cholesterol-HDL ratio, triglycerides, and creatine kinase).

The serum dioxin analyses of the hepatic enzymes found significant positive associations with ALT and GGT, but the findings were not significant for the other enzymes. The lipid indices were associated significantly and consistently with dioxin. The analyses of the variable triglycerides showed strong positive associations with both the initial levels of dioxin and the current serum levels; this variable is highly sensitive to body fat. Cholesterol, HDL, and the cholesterol-HDL ratio also showed significant associations with dioxin.

Initial dioxin level was associated with a significantly increased risk of an abnormally high level for several of the laboratory variables (AST, ALT, GGT, and the cholesterol-HDL ratio) in Ranch Hands who had reported no exposure to degreasing chemicals. This pattern is puzzling since it contradicts a synergistic effect of degreasing chemicals and dioxin exposure. The relative risk for these variables was not significant for Ranch Hands who had reported exposure to degreasing chemicals.

In summary, the gastrointestinal analyses did not indicate that the historical liver conditions were associated with dioxin at this time. However, laboratory results showed a consistent pattern suggestive of a subclinical effect on lipid metabolism, possibly related to the positive association between dioxin and percent body fat that was observed in the general health assessment.

## **Dermatologic Assessment**

The dermatologic evaluation was based on verified questionnaire data on the occurrence and location of acne (lifetime and relative to SEA tour). These data were supplemented with eight variables derived from the physical examination: comedones, acneiform lesions, acneiform scars, depigmentation, inclusion cysts, hyperpigmentation, other abnormalities, and a dermatology index. The "other abnormalities" variable included jaundice, spider angiomas, palmar erythema, palmar keratoses, actinic keratoses, petechiae, ecchymoses, conjunctival abnormality, oral mucosal abnormality, fingernail abnormality, toenail abnormality, dermatographia, cutis rhomboidalis, nevus, and other abnormalities. The dermatology index was based on the presence of comedones, acneiform lesions, acneiform scars, and inclusion cysts.

The clinical endpoint, chloracne, has been linked conclusively to topical dioxin exposure in other studies. No evidence of active chloracne has been detected at any of the three AFHS examination cycles. This is not surprising since the concentrations of TCDD exposure in Ranch Hands probably were much less than the concentrations needed to produce overt lesions, based on animal and human studies. Recognizing the remote possibility that chloracne may have occurred in acute form and been resolved, the physical examination emphasized chronic cutaneous conditions, such as scarring and pigmentation, which are complications of all forms of acne.

Dermatologic endpoints were not consistently associated with dioxin concentrations. The adjusted current dioxin and time since tour analyses displayed several statistically significant findings, but they were not supported by the adjusted initial dioxin analyses or the adjusted categorized current dioxin results. The adjusted current dioxin and time since tour analyses under the maximal assumption for Ranch Hands with a later tour of duty in Vietnam (time since tour  $\leq 18.6$  years) showed significant or marginally significant positive associations between current levels of dioxin and the occurrence of acne and several of the other acne-related physical examination variables after service in SEA. The corresponding adjusted relative risks for Ranch Hands with an early tour (time since tour  $> 18.6$  years) were either not significant or were significantly less than 1. Under the minimal assumption (but not the maximal), current levels of dioxin were associated with an increased risk of acne on the temples, eyes, and ears for Ranch Hands with an early tour.

The adjusted initial dioxin analyses found a significantly increased risk of hyperpigmentation abnormalities under the maximal assumption, but the adjusted relative risk was not significant under the minimal assumption. The questionnaire variables were not associated significantly with initial dioxin in the adjusted analyses. The adjusted categorized current dioxin results did not find that Ranch Hands in the high current dioxin category differed significantly with Comparisons in the background current dioxin category for any of the variables analyzed.

### Cardiovascular Assessment

The cardiovascular assessment was based on reported and verified heart disease (essential hypertension, overall heart disease, and myocardial infarction) and the measurement of central cardiac function and peripheral vascular function. The analyses of central cardiac function examined systolic blood pressure, heart sounds, and several variables from the electrocardiograph (ECG) readings (overall interpretation, right bundle branch block, left bundle branch block, nonspecific ST- and T-wave changes, bradycardia, arrhythmia, and other diagnoses). The evaluation of peripheral vascular function was based on diastolic blood pressure, fundoscopic examination of small vessels, carotid bruits, and manual palpation of the radial, femoral, popliteal, dorsalis pedis, and posterior pulses.

Diabetes is a major risk factor for the development of cardiovascular disease. The cardiovascular assessment excluded diabetics from most analyses so that the serum dioxin findings would be based on cardiovascular endpoints independent of a diabetes-related etiology. Additional analyses based on diabetics only were done for myocardial infarction and leg pulses.

An increased risk of cardiovascular disease was not associated with dioxin levels. There was a significantly increased risk of essential hypertension for Ranch Hands in the high current dioxin category relative to Comparisons in the background current dioxin category, when the effect of body fat was not considered. Because body fat is associated with dioxin levels, adjustment for body fat could mask a dioxin effect. By contrast, the analyses of verified heart disease (excluding essential hypertension) found that the adjusted relative risk was significantly less than 1 for Ranch Hands in the high current dioxin category; the association with initial dioxin also exhibited a significantly decreased risk under the maximal assumption. In the assessment of central cardiac function, the analyses of systolic blood pressure in its continuous form displayed significant associations with dioxin when the effect of body fat was not considered, but the corresponding discrete analyses did not show a significant increase in the prevalence of abnormally high levels of systolic blood pressure ( $>140$  mm Hg). By contrast, the adjusted analyses for "other ECG diagnoses" found significantly decreased risks in the adjusted current dioxin and time since tour analyses and in the adjusted categorized current dioxin analyses. Longitudinal analyses of the overall ECG displayed significant negative associations with dioxin.

The assessment of peripheral vascular function found significant associations between dioxin and decreases in the peripheral pulses. The adjusted categorized current dioxin analyses showed that Ranch Hands in the high current dioxin category had significantly more peripheral pulse abnormalities than Comparisons in the background current dioxin category, although Ranch Hands in the low current dioxin category had the most peripheral pulse abnormalities. Consistent with the systolic blood pressure findings, the adjusted mean diastolic blood pressure was significantly higher for Ranch Hands in the high current dioxin category relative to the background current dioxin category when the effect of body fat was not considered. However, the corresponding discrete analysis did not show a significantly increased risk of an abnormally high level of diastolic blood pressure ( $>90$  mm Hg).

The cardiovascular findings in this report offered no consistent evidence of an adverse dioxin effect. At present, there is no evidence that humans experience cardiovascular sequelae related to chronic low-dose dioxin exposure. However, the blood pressure and pulse observations could represent early subclinical effects and emphasize the need for continued evaluation in subsequent phases of the study.

### **Hematologic Assessment**

The hematologic assessment examined nine laboratory variables: red blood cell count, white blood cell (WBC) count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, and prothrombin time. These variables can be used to indicate hematopoietic disease and, perhaps more often, to alert the clinician to the presence of disease in other organ systems.

The hematologic results revealed no evidence that overt hematopoietic toxicity was related to dioxin exposure. The WBC count revealed statistically significant increases consistent with a dose-response effect in all three models; consistent significant results were not found for the other variables. The adjusted categorized current dioxin analyses for platelet count found a significantly increased risk of an elevated platelet count for Ranch Hands in the high current dioxin category relative to the Comparisons in the background current dioxin category. These findings suggest the presence of a low-level, chronic



inflammatory response that may not be considered clinically significant, but underscores the need for continued surveillance.

### **Renal Assessment**

History of kidney disease and five laboratory variables (urinary protein, urinary occult blood, urinary white blood cell count, blood urea nitrogen, and urine specific gravity) were analyzed in the assessment of renal function. The statistical analyses did not indicate any renal health detriment related to dioxin. Under the maximal assumption of model 1 (but not the minimal), the initial dioxin analyses found a significantly increased risk of urinary occult blood cells, but results were not significant for the model 2 and model 3 analyses.

Statistically significant results were not noted for the other variables. These results are consistent with the renal assessments from the previous AFHS reports, which did not find significant differences between the Ranch Hand and Comparison groups.

### **Endocrine Assessment**

The endocrine assessment focused on thyroid, testicular, and pancreatic functions. Seven laboratory variables were analyzed: T<sub>3</sub> % uptake, thyroid stimulating hormone (TSH), follicle stimulating hormone, testosterone, fasting glucose, 2-hour postprandial glucose, and a composite diabetes indicator. Physical examination data for the thyroid gland and the testes also were evaluated.

In the evaluation of thyroid function, the categorized current dioxin analyses found a significant decrease in the mean T<sub>3</sub> % uptake and a significant increase in the mean TSH for Ranch Hands in the high current dioxin category relative to Comparisons in the background current dioxin category. There was a significant negative correlation between initial dioxin and T<sub>3</sub> % uptake. Though these results were consistent with subclinical decreases in thyroid function related to dioxin exposure, the magnitude of the differences between Ranch Hands in the higher and lower dioxin categories were not considered physiologically significant. In addition, the discrete analyses for these variables did not indicate that dioxin was associated with an increase in the prevalence of abnormal levels.

Decreased testicular size was associated significantly with initial and current levels of serum dioxin. The clinical meaning of this finding is unclear at this time. The discrete analyses of testosterone did not find a significant association between dioxin and abnormally low levels of serum testosterone (<260 ng/dl), but the continuous analyses detected a significant negative association with dioxin when the effect of body fat was not considered. Fertility and other reproductive outcomes will be assessed in a separate report.

Initial dioxin and current levels of serum dioxin both were associated highly with an increased risk of diabetes. Significant positive associations were noted for the analyses of fasting glucose and 2-hour postprandial glucose. The results clearly established a strong association between glucose intolerance and dioxin, but concluding that dioxin directly causes diabetes would be premature. Clinically, obesity is recognized as the most common cause of adult-onset diabetes mellitus. The general health assessment revealed a strong positive association between serum dioxin levels and percent body fat, but the diabetes findings remained significant after adjusting for body fat. Whether these findings imply an increase in diabetes or the earlier appearance of clinical diabetes in susceptible men remains an open

question. The basis of these relationships will be investigated during subsequent phases of this study.

### **Immunologic Assessment**

The immunologic assessment analyzed composite skin-reaction test results in addition to various laboratory measurements consisting of cell surface marker studies, three groups of functional stimulation tests, and quantitative immunoglobulins. The evaluated indices of immunologic capability provide a comprehensive reflection of in vivo and in vitro immune function in the study population. Because of the complexity of the assays and the expense of the immunologic tests, a random sample of approximately 40 percent of the participants was chosen to receive these tests. Of the subset of participants chosen for immunologic testing and assayed for serum dioxin levels, 9.9 percent were diabetic. This percentage was not significantly different from the percentage of assayed participants not selected for immunologic testing (8.3%).

Previously reported Ranch Hand and Comparison group contrasts based on the 1987 physical examination found that significantly more Ranch Hands than Comparisons had possibly abnormal reactions on the delayed hypersensitivity skin-test response, but results for the laboratory variables revealed no medically important differences. In this report, the serum dioxin analyses for the composite skin test diagnosis did not support a dioxin-related effect, suggesting that the previously noted group difference may not be related to dioxin.

Evaluation of the immunoglobulins found a significant association between initial dioxin and IgA increases, consistent with a subtle inflammatory response. The analyses of the other immunoglobulins (IgG and IgM) did not indicate the presence of any dioxin-related effects. Analyses for the other laboratory variables revealed several statistically significant findings, but they either were internally inconsistent or were not in a direction expected in an impaired immune system. In conclusion, the immunologic assessment did not exhibit clinically significant trends related to the current serum dioxin level or the initial level.

### **Pulmonary Assessment**

The pulmonary assessment was based on the verified histories for five self-reported illnesses, five physical examination variables, and seven laboratory measurements from the pulmonary function tests.

Analyses of pulmonary disease history found no evidence of a dioxin effect on the five verified respiratory illnesses studied (asthma, bronchitis, pleurisy, pneumonia, and tuberculosis). Consistent with the findings from the previous report of the 1987 examination data, none of these conditions was significantly associated with either the initial level or the current level of serum dioxin.

The five physical examination variables were hyperresonance, dullness, wheezes, rales, and a composite of these variables (denoted as thorax and lung abnormalities). These variables can provide valuable clues to the presence of pulmonary disease, but are of limited use in confirming a diagnosis because of their lack of specificity. Wheezes and hyperresonance, for example, will occur in obstructive airway disease, in asthma, or in chronic obstructive pulmonary disease (COPD or emphysema) secondary to cigarette use.

The dioxin analyses of the physical examination variables detected increased risks of statistical significance or marginal significance for each variable in at least one adjusted analysis. The adjusted model 3 analyses found that the relative risk for each variable (other than dullness, which had only three abnormalities) was significantly or marginally more than 1 for Ranch Hands in the high current dioxin category relative to Comparisons in the background current dioxin category. The previous 1987 examination finding that Ranch Hands had marginally more thorax and lung abnormalities than Comparisons in an adjusted analysis is consistent with these results.

The laboratory variables evaluated for this study were x-ray interpretation, forced vital capacity (FVC), forced expiratory volume at 1 second (FEV<sub>1</sub>), forced expiratory flow maximum (FEFmax), the ratio of observed FEV<sub>1</sub> to observed FVC, loss of vital capacity, and obstructive abnormality. The x ray, when normal, is highly reliable for excluding pulmonary parenchymal disease. The spirometric indices are designed to measure lung volume (FVC) and respiratory air flow (FEV), and are used to help diagnose restrictive and obstructive disease. Restrictive disease is characterized by reduced vital capacity as seen in interstitial fibrosis or reduced lung volume after surgical resection. The flow dependent indices (FEV<sub>1</sub> and FEFmax) are abnormally prolonged in obstructive airways disease, usually COPD.

Serum dioxin was not associated significantly with the x-ray interpretation. By contrast, the analyses of the spirometric indices were often significant, but the differences in the mean levels were not clinically important. Initial dioxin was significantly associated with decreases in FVC, FEV<sub>1</sub>, and FEFmax in addition to a significant increase in the ratio of observed FEV<sub>1</sub> to observed FVC. Adjusted results for the model 2 and model 3 analyses also displayed significant findings for these variables. In clinical practice, obesity is known to cause a reduction in vital capacity. The results described here may be due in part to the significant positive association between serum dioxin and percent body fat that is detailed in the general health assessment. Accordingly, interpretation of these results must await further evaluation of the dioxin and body fat relationship.

In the longitudinal analysis of the ratio of observed FEV<sub>1</sub> to observed FVC, there was a significant positive association with current dioxin and a significant difference among the current dioxin categories.

### **Extrapolation of Results**

Extrapolation of the serum dioxin results to the general population of ground troops who served in Vietnam is difficult because Ranch Hand and ground-troop exposure situations were quite different. Based on serum dioxin testing results done by other researchers, nearly all ground troops tested have current levels of dioxin similar to background levels. Even ground troops who served in herbicide-sprayed areas of Vietnam had current levels indistinguishable from levels in men who never left the United States. The AFHS subgroup most like the ground troops in terms of current dioxin levels are Ranch Hands who currently have background levels of dioxin (10 ppt or less, designated as the "unknown" current dioxin category in the model 3 analyses). Therefore, if the results of the AFHS are applied to the general population of Vietnam veterans, the focus should be on the unknown Ranch Hand versus background Comparison contrast in the model 3 analyses. However, extrapolating the

results of these analyses to Vietnam veterans should still be made cautiously. There may be demographic distinctions between the unknown group of Ranch Hands and other Vietnam veterans that may be health-related. In general, the adjusted model 3 analyses found that Ranch Hands in the unknown current dioxin category did not show a significant health detriment relative to Comparisons in the background current dioxin category. This was particularly true for the variables that exhibited a significant high versus background contrast.

## SUMMARY

The serum dioxin analyses in this report detected significant associations with lipid-related health indices. In particular, diabetes and body fat were associated positively with dioxin. Cholesterol, HDL, the cholesterol-HDL ratio, and 2-hour postprandial glucose also were associated significantly with dioxin. Erythrocyte sedimentation rate, WBC count, IgA, and platelet count were positively associated with dioxin, suggesting the presence of a chronic dose-related inflammatory process. Other variables, such as the spirometric indices in the pulmonary assessment and benign systemic neoplasms in the malignancy assessment, showed significant associations with dioxin that may be related to the body fat results (approximately 75% of the benign systemic neoplasms in Ranch Hands and 70% in Comparisons were lipomas). These findings and their possible relationship to dioxin elimination will be explored in future examination cycles. The serum dioxin analyses also revealed a significant positive association between dioxin and decreased testicular size, but the importance of this finding is unclear (fertility and other reproductive outcomes will be assessed in a separate report). Results for the other variables revealed no consistent pattern (within or across clinical areas) indicative of a health detriment due to dioxin exposure.

Occasionally there was a significant finding in the analysis of a variable in its continuous form, but the corresponding results for the discrete analysis were not significant. Small but significant mean differences in a continuously measured health variable when there are no corresponding differences in the percentage of abnormal tests are difficult to assess in any study. For example, in the discrete analysis of serum testosterone, abnormally low levels were not associated significantly with dioxin. However, the adjusted continuous analysis found a significant negative association between dioxin and testosterone when the effect of body fat was not considered. The continuous and discrete analyses of systolic and diastolic blood pressure also exhibited conflicting results. Observations such as these could represent an early subclinical effect, or they could be the result of a multiple-testing artifact. Significant trends in the mean with increasing levels of dioxin are interpreted as a dioxin-related effect if a corresponding trend is seen in the proportion above or below the normal range. These observations emphasize the importance of continued evaluation of a broad spectrum of health endpoints in the subsequent physical examination phases of the AFHS.

The graphical displays for fasting and 2-hour postprandial glucose, AST, cholesterol, the cholesterol/HDL ratio, and diastolic blood pressure show a remarkable similarity in the pattern of results between the Comparisons and those Ranch Hands with dioxin levels below 15 ppt. Often, a dioxin-related increase is seen in the Comparisons as well as the Ranch Hands, without an obvious threshold. The medical importance of these observations is not clear, but these data suggest that there may not be a threshold for a subtle dioxin effect, even at levels considered to be at or near background.

In summary, many of the findings in this report reveal a consistent relationship between dioxin and body fat. Two hypotheses may explain the observed relationships. In one, dioxin could cause an increase in body fat, or the level of body fat could influence the dioxin decay rate, which, in turn, alters physiologic outcomes, such as blood pressure, serum lipid alterations, and blood sugar levels. An alternative hypothesis involves dioxin as a direct cause of two or more of the observed endpoints, including body fat. Whether dioxin causes these observed effects directly or is a step in an extended causal pathway cannot be determined from these data. Additional analyses following the next physical examination scheduled for 1992 may help resolve this question.