

TABLE 17-23. (Continued)

**Summary of Categorized Current Dioxin Analyses  
for Pulmonary Variables  
(Ranch Hands and Comparisons)**

Variable	All	Adjusted		
		Unknown versus Background	Low versus Background	High versus Background
<b>Questionnaire</b>				
Asthma (D)	NS	+0.033	NS	NS
Bronchitis (D)	** (NS)	** (NS)	** (NS)	** (ns)
Pleurisy (D)	NS	ns	ns	NS
Pneumonia (D)	NS	ns	ns	ns
Tuberculosis (D)	NS	NS	ns	ns
<b>Physical Examination</b>				
<b>Thorax and Lung</b>				
Abnormalities (D)	NS*	ns	NS	+0.037
Hyperresonance (D)	NS	ns	ns	NS*
Dullness (D)	--	--	--	
Wheezes (D)	NS	NS	NS	NS*
Rales (D)	NS	ns	ns	+0.049
<b>Laboratory</b>				
X-Ray Interpretation (D)	NS	ns	ns	NS
FVC <sup>a</sup> (C)	** (<0.001)	** (NS*)	** (ns)	** (<0.001)
FEV <sub>1</sub> <sup>a</sup> (C)	** (NS*)	** (NS)	** (ns)	** (ns*)
FEFmax <sup>a</sup> (C)	0.026	NS	ns*	ns
Ratio of Observed FEV <sub>1</sub> to Observed FVC (C)	<0.001	-0.042	ns	+<0.001
Loss of Vital Capacity <sup>b</sup> (D)	NS*	ns	NS	+0.036
Loss of Vital Capacity <sup>c</sup> (D)		NS*	NS	NS
Obstructive Abnormality <sup>b</sup> (D)	NS*	+0.020	NS	ns
Obstructive Abnormality <sup>c</sup> (D)		NS	NS	ns

<sup>a</sup>Negative difference considered adverse for this variable.

<sup>b</sup>Mild contrasted with none for the last three columns.

<sup>c</sup>Moderate/severe contrasted with none for the last three columns.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.

-: Difference in means negative for continuous analysis.

--: Analysis not performed due to sparse number of abnormalities.

**TABLE 17-23. (Continued)**

**Summary of Categorized Current Dioxin Analyses  
for Pulmonary Variables  
(Ranch Hands and Comparisons)**

NS/ns: Not significant ( $p>0.10$ ).

NS\*/ns\*: Marginally significant ( $0.05 < p \leq 0.10$ ).

\*\* (NS)/\*\* (ns): Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); not significant when interaction is deleted; refer to Appendix Table P-1 for a detailed description of this interaction.

\*\* (NS\*)/\*\* (ns\*): Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); marginally significant when interaction is deleted; refer to Appendix Table P-1 for a detailed description of this interaction.

\*\* (<0.001): Categorized current dioxin-by-covariate interaction ( $0.01 < p \leq 0.05$ ); significant ( $p < 0.001$ ) when interaction is deleted; refer to Appendix Table P-1 for a detailed description of this interaction.

Note: P-value given if  $p \leq 0.05$ .

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference in means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference in means negative for continuous analysis; a capital "NS" in the first column does not imply directionality; a capital "NS" for loss of vital capacity and obstructive abnormality does not imply directionality due to log-linear analysis.

less than 1 ( $p=0.062$ ). Under the minimal assumption, there was a marginally significant increased risk of pleurisy ( $p=0.090$ ). No significant association between initial dioxin and pneumonia nor between initial dioxin and tuberculosis was exhibited in both the unadjusted and adjusted analyses.

#### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

The interaction between current dioxin and time since tour was not significant for any of the questionnaire variables in the unadjusted analyses of the minimal and maximal cohorts. For time less than or equal to 18.6 years, however, the risk of bronchitis was significantly less than 1 ( $p=0.044$ ).

In the adjusted analysis of bronchitis, there was a significant interaction among current dioxin, time, and race for both cohorts (minimal,  $p=0.015$ ; maximal,  $p<0.001$ ). There was also a significant interaction among current dioxin, time, and race in the analysis of pleurisy (minimal,  $p<0.001$ ; maximal,  $p=0.007$ ). For both of these interactions, the examination of the race strata was inconclusive because of the sparseness of occurrences in the Black stratum.

#### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The overall contrasts of the four current dioxin categories showed no significant relationship between the categorized current dioxin level and the questionnaire variables in the unadjusted analyses. However, in the unknown versus background contrast, an increased risk of asthma was significant ( $p=0.040$ ).

In the adjusted analysis of asthma, the relative risk in the unknown versus background contrast remained significantly greater than 1 ( $p=0.033$ ). In the adjusted analysis of bronchitis, there was a significant interaction between categorized current dioxin and age ( $p=0.043$ ), but the overall contrast was not significant within both age strata. There was, however, a marginally significant increased risk of bronchitis when contrasting the younger Ranch Hands in the unknown current dioxin category with the younger Comparisons in the background category ( $p=0.057$ ). There was also a significant risk of bronchitis that was less than 1 when contrasting the older Ranch Hands in the high category with the older Comparisons in the background category ( $p=0.050$ ). Without this interaction in the model, the overall contrast was not significant.

#### **Physical Examination Variables**

Both unadjusted and adjusted analyses were performed on the following physical examination variables: thorax and lung abnormalities, hyperresonance, dullness, wheezes, and rales. No analyses were performed on asymmetric expansion since this condition was not diagnosed in any of the patients. Dullness was also excluded from the current dioxin and time since tour and the categorized current dioxin analyses because of the sparse number of occurrences.

#### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

In the unadjusted analyses, there were no significant associations between the physical examination variables and initial dioxin, except under the analysis of dullness. In this analy-

sis there was a marginally significant increased risk of dullness under the maximal assumption ( $p=0.094$ ).

In the adjusted analysis of thorax and lung abnormalities there was a marginally significant increased risk under the minimal assumption ( $p=0.088$ ) and a significant increased risk under the maximal assumption ( $p=0.022$ ). There were also marginally significant increased risks of hyperresonance ( $p=0.076$ ) and dullness ( $p=0.051$ ) under the maximal assumption. Under both the minimal and maximal assumptions, there was a significant increased risk of wheezes in the adjusted analysis ( $p=0.034$  for both cohorts).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted analyses of all physical examination variables, the association with current dioxin did not differ between the time since tour strata, under both assumptions.

In the adjusted minimal analysis of thorax and lung abnormalities there was a significant interaction among current dioxin, time, and age ( $p=0.012$ ). The current dioxin-by-time interaction was not significant within either age stratum, but there was a significant increased risk of thorax and lung abnormalities for older Ranch Hands whose time since tour did not exceed 18.6 years ( $p=0.038$ ). Without the current dioxin-by-time-by-age interaction in the model, there was a marginally significant increased risk when time was restricted to 18.6 years or less ( $p=0.100$ ). Under the maximal assumption the increased risk of thorax and lung abnormalities was significant for Ranch Hands whose time since tour was greater than 18.6 years ( $p=0.030$ ). There was also a significant increased risk of hyperresonance for the same subgroup of Ranch Hands ( $p=0.027$ ).

Within the adjusted minimal analysis of wheezes there was a significant interaction among current dioxin, time, and age ( $p=0.018$ ). The relative risks did not differ significantly between the two time strata for the younger Ranch Hands, but for the older Ranch Hands, the risk of wheezes was significantly greater than 1 ( $p=0.026$ ) when time was no more than 18.6 years and was less than 1, but not significant, when time was greater than 18.6 years. When this interaction was removed from the model, there was a marginally significant increased risk of wheezes for Ranch Hands in the minimal cohort whose time since tour did not exceed 18.6 years ( $p=0.079$ ). There was also a marginally significant increased risk of wheezes for Ranch Hands in the maximal cohort whose time since tour was greater than 18.6 years ( $p=0.074$ ).

### ***Model 3: Ranch Hands and Comparisons by Current Dioxin Category***

The overall contrasts of the four current dioxin categories were not significant for any of the physical examination variables in the unadjusted analyses. A marginally significant increased risk was observed for thorax and lung abnormalities when contrasting the Ranch Hands in the low current dioxin level with the Comparisons in the background current dioxin level ( $p=0.097$ ).

In the adjusted analysis of thorax and lung abnormalities the overall contrast was marginally significant ( $p=0.096$ ). The percentages of abnormalities in the current dioxin categories that consisted of Ranch Hands (i.e., unknown, low, and high) exceeded the percentage in the background category. Under the high versus background contrast, there

were significant increased risks of thorax and lung abnormalities ( $p=0.037$ ) and rales ( $p=0.049$ ) and marginally significant increased risks of hyperresonance ( $p=0.086$ ) and wheezes ( $p=0.092$ ).

## Laboratory Variables

Continuous analyses were performed on FVC, FEV<sub>1</sub>, FEFmax, and the ratio of observed FEV<sub>1</sub> to observed FVC. X-ray interpretation, loss of vital capacity (restrictive abnormality), and obstructive abnormality were analyzed as discrete variables.

### ***Model 1: Ranch Hands - Log<sub>2</sub> (Initial Dioxin)***

There was a significant positive association between initial dioxin and the ratio of observed FEV<sub>1</sub> to observed FVC under the minimal assumption ( $p=0.001$ ). Under the maximal assumption there was a significant negative association between initial dioxin and FVC ( $p<0.001$ ), initial dioxin and FEFmax ( $p=0.021$ ), and a significant positive association between initial dioxin and the ratio of observed FEV<sub>1</sub> to observed FVC ( $p<0.001$ ). Loss of vital capacity had a marginally significant overall association with the initial dioxin under the maximal assumption ( $p=0.051$ ) and obstructive abnormality had a significant overall association under both assumptions (minimal,  $p=0.018$ ; maximal,  $p=0.016$ ).

In the adjusted minimal analyses of both FVC and FEV<sub>1</sub> there was a significant interaction between initial dioxin and current cigarette smoking (FVC:  $p=0.013$ ; FEV<sub>1</sub>:  $p=0.029$ ). For FVC, the association with initial dioxin was significantly negative for those who never smoked ( $p=0.003$ ) and increased with increased current cigarette use. The same trend was exhibited in the analysis of FEV<sub>1</sub>, with the association for those who never smoked being significantly negative ( $p=0.023$ ). When the interaction was removed from the analysis of FVC, there was a significant negative association with initial dioxin ( $p=0.028$ ). In the adjusted minimal analysis of the ratio of observed FEV<sub>1</sub> to observed FVC, there was also a significant positive association with initial dioxin ( $p=0.022$ ).

In the adjusted maximal analysis of the continuous variables, there was a significant negative association with initial dioxin for FVC ( $p<0.001$ ), FEV<sub>1</sub> ( $p=0.026$ ), and FEFmax ( $p=0.014$ ), and a significant positive association with FEV<sub>1</sub>/FVC ( $p<0.001$ ). The overall contrast in the adjusted analysis of loss of vital capacity was marginally significant under the minimal assumption ( $p=0.052$ ) and significant under the maximal assumption ( $p=0.011$ ).

In the longitudinal analysis of the ratio of observed FEV<sub>1</sub> to observed FVC, a marginally significant positive association was exhibited between initial dioxin and the change in the ratio from 1982 to 1987 (minimal:  $p=0.093$ ; maximal:  $p=0.100$ ).

### ***Model 2: Ranch Hands - Log<sub>2</sub> (Current Dioxin) and Time***

In the unadjusted analyses of the minimal and maximal cohorts, the current dioxin-by-time since tour interaction was not significant for any of the laboratory variables. However, under the minimal analysis, there was a marginally significant positive association between current dioxin and FEFmax ( $p=0.085$ ) and a significant positive association between current dioxin and the ratio of observed FEV<sub>1</sub> to observed FVC ( $p=0.045$ ) when time was no more than 18.6 years. There was also a significant positive association between current dioxin and the ratio of observed FEV<sub>1</sub> to observed FVC ( $p=0.004$ ) when time was greater than 18.6

years. The overall contrast for the analysis of obstructive abnormality within this time stratum was marginally significant ( $p=0.083$ ).

Under the maximal assumption, when time was no more than 18.6 years, current dioxin had a significant negative association with FVC ( $p=0.003$ ) and FEFmax ( $p=0.013$ ), and a positive association with the ratio of observed FEV<sub>1</sub> to observed FVC ( $p=0.005$ ). When time was greater than 18.6 years, there was also a significant positive association between current dioxin and the ratio of observed FEV<sub>1</sub> to observed FVC ( $p<0.001$ ). The overall contrast in the analysis of obstructive abnormality within this time stratum was also significant ( $p=0.044$ ).

After the models were adjusted for covariates, the interaction between current dioxin and time remained nonsignificant for all of the variables, except in the minimal analysis of FEFmax in which the interaction became marginally significant ( $p=0.100$ ). In this analysis, the association with current dioxin was negative for time less than or equal to 18.6 years ( $p=0.063$ ), and positive but nonsignificant for time greater than 18.6 years. Under the minimal assumption, there were negative associations between current dioxin and FVC ( $p=0.024$ ) and between current dioxin and FEV<sub>1</sub> ( $p=0.085$ ) when time was no more than 18.6 years and a positive association between current dioxin and the ratio of observed FEV<sub>1</sub> to observed FVC ( $p=0.067$ ) when time was greater than 18.6 years.

Under the maximal assumption, for time less than or equal to 18.6 years, there was a significant negative association between current dioxin and FVC ( $p<0.001$ ), FEV<sub>1</sub> ( $p=0.014$ ), and FEFmax ( $p=0.010$ ), and a significant positive association between current dioxin and FEV<sub>1</sub>/FVC ( $p=0.034$ ). For time greater than 18.6 years, these associations were in the same direction but were only significant for FVC ( $p=0.009$ ) and the ratio of observed FEV<sub>1</sub> to observed FVC ( $p=0.005$ ). The overall contrast for loss of vital capacity was also significant within the stratum containing Ranch Hands whose time since tour did not exceed 18.6 years ( $p=0.019$ ).

The current dioxin-by-time since tour interaction was nonsignificant in the longitudinal analysis of the ratio of observed FEV<sub>1</sub> to observed FVC. However, there was a significant positive association between the ratio and current dioxin for time greater than 18.6 years in the maximal cohort ( $p=0.018$ ).

### **Model 3: Ranch Hands and Comparisons by Current Dioxin Category**

The overall contrast of the four current dioxin categories was significant for the analyses of FVC ( $p<0.001$ ) and the ratio of observed FEV<sub>1</sub> to observed FVC ( $p<0.001$ ) and was marginally significant for the analysis of FEFmax ( $p=0.077$ ). Therefore, in each of these analyses, there was a significant, or marginally significant, difference in the means among the four current dioxin categories. In the analyses of FVC, FEV<sub>1</sub>, and FEFmax, the mean in the unknown category was greater, although not necessarily significant, than the mean in the background category. The means in the low and high categories were less than the mean in the background category. In the analysis of the ratio of observed FEV<sub>1</sub> to observed FVC this trend was reversed, with the unknown mean less than the background mean and the high

mean greater than the background mean. The overall contrast in the analysis of obstructive abnormality was also significant ( $p=0.002$ ).

In the adjusted analyses of FVC and  $FEV_1$ , there was a significant interaction between the categorized current dioxin and current cigarette smoking (FVC:  $p=0.018$ ;  $FEV_1$ :  $p=0.039$ ). In the analysis of FVC, the overall contrast was significant for nonsmokers ( $p<0.001$ ) and former smokers ( $p=0.005$ ) and was marginally significant for those who smoke no more than 20 cigarettes per day ( $p=0.094$ ). Without this interaction in the model, the overall contrast was significant ( $p<0.001$ ).

In the analysis of  $FEV_1$ , the only significant overall contrast was for nonsmokers ( $p=0.034$ ). After the interaction was removed from this model, the overall contrast was marginally significant ( $p=0.091$ ). The overall contrast was significant in the adjusted analyses of FEFmax ( $p=0.026$ ) and the ratio of observed  $FEV_1$  to observed FVC ( $p<0.001$ ). The trends in the means relative to the background category remained the same as in the unadjusted analyses of these four continuous variables. The overall contrasts were marginally significant in the adjusted analyses of loss of vital capacity ( $p=0.052$ ) and obstructive abnormality ( $p=0.083$ ).

In the longitudinal analysis, the change in the ratio of observed  $FEV_1$  to observed FVC from 1982 to 1987 differed significantly among the four current dioxin categories ( $p=0.033$ ). The change in the ratio was significantly greater for Ranch Hands in the high category than for Comparisons in the background category ( $p=0.032$ ).

## CONCLUSION

In general, there was no association between initial dioxin and the discrete variables. For the continuous variables, however, there appeared to be a negative association with initial dioxin, especially under the maximal assumption. The associations with current dioxin did not differ significantly between the two time strata for any of the variables, under both assumptions. In the categorized current dioxin analyses, the percentage of abnormalities did not differ significantly among the four current dioxin categories for any of the questionnaire and physical examination variables, except under the adjusted analysis of thorax and lung abnormalities. In this case, Ranch Hands in the low and high categories had a higher percentage of abnormalities than Comparisons in the background category, but Ranch Hands in the unknown category had a lower percentage than the Comparisons in the background category. For the continuous variables, the means differed among the current dioxin categories. For FVC,  $FEV_1$ , and FEFmax, the mean for the Ranch Hands in the unknown category tended to be greater than the mean for the Comparisons in the background category, but the means for the low and high categories were less than the mean for the background category. In the analysis of the ratio of observed  $FEV_1$  to observed FVC this trend was reversed.

In the longitudinal analysis of the ratio of observed  $FEV_1$  to observed FVC, there was a significant positive association with current dioxin and a significant difference among the current dioxin categories.

In summary, the historical, physical examination, and laboratory data analyzed in the current section revealed no evidence for an increased incidence of pulmonary disease in the Ranch Hand cohort in relation to the body burden of dioxin. Analysis of two laboratory variables, FVC and the ratio of observed  $FEV_1$  to observed FVC, yielded results that were consistent with subtle dose-response effects related to the body burden of dioxin in Ranch Hands. Body habitus and, more specifically, percent body fat may play a role in these associations between dioxin and pulmonary function indices.

## CHAPTER 17

### REFERENCES

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## 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 angioma, 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 1.5 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.

## CHAPTER 19

### FUTURE DIRECTIONS

The development of a method to determine levels of dioxin in serum has been a significant enhancement to this study. This procedure permitted the study scientists to develop a measure of exposure for each individual that did not require making assumptions of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure based on a surrogate indicator (developed from available historical data on fixed-wing spray missions used to disseminate Herbicide Orange, Herbicide Purple, Herbicide Pink, and Herbicide Green). The method provided the opportunity to move from relatively simple group contrasts of Ranch Hands and Comparisons to detailed analyses of dose response on an individual basis.

While this breakthrough has led to dramatic improvements in the study, it also has highlighted opportunities for further refinements to the study that will be implemented for the next phase of the study scheduled for 1992. These refinements in exposure assessment will include an evaluation of the pattern of dioxin isomers in the serum of a selected group of participants. These participants would include all Comparisons with 1987 TCDD levels above 20 ppt and a random sample of Ranch Hands. Additionally, serum samples will be collected for dioxin assays from all participants who did not provide blood for testing in 1987 or whose assays did not result in a valid determination in the laboratory. The Air Force also plans to obtain serum samples at the 1992 examination on a selected group of Ranch Hands so that a third data point will be available in the determination of dioxin half-life over the 10 years since 1982. These data, coupled with the results of half-life studies in men exposed to TCDD in Seveso, Italy, in 1976, will be used to assess the validity of the first-order pharmacokinetics assumption for dioxin elimination in humans.

Data on weight changes and intervening illness also will be included in half-life determinations for the 1992 examination. If the first-order elimination assumption is supported by the Seveso data, a specific half-life determination for each individual will be determined for use in the statistical analyses rather than the single value used for everyone in this report.

Modifications to the format of the physical examination also are envisioned for 1992. These include the determination of serum insulin levels, Doppler studies of peripheral arterial circulation, replacement of the T<sub>3</sub> % uptake with a refined methodology to measure the thyroid stimulating hormone accurately in both hyperthyroid and hypothyroid conditions, and the collection of data on the presence of claudication and peripheral vascular insufficiency. In addition, the components of the immunological assessment will be evaluated to ensure that the most current measures of immunological function are used.