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17 IMMUNOLOGIC ASSESSMENT

17.1 INTRODUCTION

17.1.1 Background

Of the many chemical compounds known to cause immune system dysfunction in laboratory animals, the polyhalogenated aromatic hydrocarbons have been the most extensively studied and, among these, 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) has proven to be the most toxic. Since the early 1970s, when dioxin was shown to cause marked involution of the thymus gland in experimental animals (1–4), the extensive body of literature pertinent to dioxin-induced immunotoxicity has been summarized in several review articles (5–10).

In laboratory animals, dioxin has proven to have a wide range of toxic effects on all components of the immune system, including direct thymotoxic effects, particularly on the epithelial cells (8, 11–14), compromised cell mediated (1, 13, 15–18) and humoral (1, 17, 19–22) immune function, impaired myelo- (23, 24) and lymphoproliferative (13, 25–27) responses, and suppressed complement activity (28–31).

The crucial role of the immune system in resistance to infection has been well established, and numerous animal studies have demonstrated that exposure to dioxin increases host susceptibility to a broad range of bacterial (19, 23, 29, 32, 33), parasitic (34), and viral (35, 36) infectious agents.

The role of the aryl hydrocarbon (Ah) receptor as a mediator in dioxin toxicity has been long recognized (37, 38) and summarized in numerous reviews (6, 39, 40). Much of the basic research in laboratory animals has focused on the role of the Ah receptor in some but not all manifestations of dioxin-induced immunotoxicity, including suppressed humoral (20, 22, 41–46) and cellular (47, 48) responses and impaired complement activity (49). Other studies have demonstrated that dioxin exposure can cause immune system responses independent of the Ah receptor (42, 43, 45, 50–52). Although the Ah receptor has been identified in several human tissues (see references 43, 51–53, and 55 in Chapter 9, General Health Assessment), the relevance of these observations to dioxin toxicity in humans remains unknown. In an attempt to provide data more relevant to humans, two laboratories have conducted experiments of the effects of dioxin on peripheral lymphocyte subpopulations in marmoset (52–56) and rhesus (57) monkeys. These studies were carried out *in vitro*, employing lymphocyte cell cultures, and *in vivo*, with single-dose injections of dioxin in various concentrations. In these experiments, the ratios of selected lymphocyte subsets varied inconsistently in response to the dose (high versus low) and duration (acute versus chronic) of exposure. In none of the *in vivo* studies did the animals demonstrate any overt illness.

The demonstration that human tonsils contain the Ah receptor (58) and the development of a tonsillar lymphocyte culture model have established a scientifically valid basis for comparison of the effects of dioxin on experimental animals and humans at the cellular level. In published results from two series of experiments, dioxin had identical effects on both human and murine B lymphocytes with dose-dependent suppression of cellular proliferation and a significant reduction in the secretion of immunoglobulins IgM and IgG (59, 60). Although the mechanism is not known, these experiments provide strong evidence that the human lymphocyte is sensitive to dioxin. These results are consistent with those reported from another laboratory investigating the effect of dioxin on human lymphocytes isolated from peripheral blood (61). As noted below, these experimental models have been applied recently to human populations exposed to dioxin (62, 63).

Immune system indices have been included in epidemiological studies of populations exposed to dioxin consequent to industrial accidents (64–72), by occupation (62, 63, 73–75), by environmental contamination (76–81), and during military service in Vietnam (82–86). Industrial accidents have resulted in the most severe human exposure to dioxin on record. In three reports published shortly after the 1976 chemical explosion in Seveso, Italy, no immune system abnormalities were found in exposed children (64, 65) or cleanup workers (66). In contrast, other investigators documented abnormal immune indices in children with chloracne (67, 68) that resolved over time and were not associated with any clinical immune deficiency illness (69, 70). Similarly, the immunologic testing abnormalities noted in a cohort of chemical workers exposed to dioxin in an industrial accident in England in 1968 were not associated with any clinical illness (71, 72).

Most of the recently published epidemiological studies have reported on the results of clinical examinations of workers who experienced significant occupational exposure to dioxin during employment at chemical factories in Germany (62, 63, 73–75). These studies, which incorporated immune system parameters in the examination protocols, are strengthened by the inclusion of serum dioxin data in the analyses. None of these studies showed any evidence in those exposed for clinical illness associated with immune system disorders nor, in relation to the body burden of dioxin, any statistically significant abnormalities in the laboratory indices.

Resident populations in the Times Beach, Missouri, area have been the subject of several studies yielding conflicting results, some of which can be attributed to methodological limitations. In two early reports, abnormalities were documented in several indices of immune function, including impaired delayed sensitivity by skin testing and nonsignificant variations in several peripheral lymphocyte subsets and ratios (76–78). In subsequent follow-up examinations of the same subjects, there were no significant differences between the exposed and control cohorts (79, 80).

A subsequent report of the subject Missouri population included serum dioxin levels that ranged from less than 20 parts per trillion (ppt) to 750 ppt. In this study, a correlation was noted between serum dioxin and an increasing percentage of CD8+ (suppressor T cells) and T₁₁+ subsets of T lymphocytes, as well as statistically nonsignificant increases in serum IgA and complement components C3 and C4 (81). As in the other Missouri studies, there was no evidence for clinical illness in the exposed cohort relative to controls.

Finally, in the 1987 and 1992 examinations of the Air Force Health Study (AFHS), multiple immunologic indices have been examined in relation to serum dioxin levels (85, 86). In the 1987 examination and, to a lesser degree, in the 1992 examination, serum IgA immunoglobulin levels were significantly higher in the Ranch Hand cohort than controls in a pattern consistent with a dose-response effect. Although of uncertain significance, this finding is of interest as one that has been noted in two other epidemiological studies cited above (74, 81) and, separately, a report of a laboratory animal study (87) that documented a selective increase in the IgA globulin fraction after a single injection of dioxin. There have been no other significant immune system differences between the Ranch Hands and Comparisons across the baseline, 1985, 1987, and 1992 examinations.

17.1.2 Summary of Previous Analyses of the Air Force Health Study

17.1.2.1 1982 Baseline Study Summary Results

Immunologic function and phenotypic marker studies were performed on 592 participants (297 Ranch Hands, 295 Comparisons) randomly selected by the terminal digit of their case number. Because of laboratory problems (e.g., fluctuating quality control and lack of simultaneous differential counts on the peripheral mononuclear cells), data could be analyzed on a group basis only.

Analyses of the cell surface markers (CD2+ or T₁₁ [T cells], CD3+ or T₃ [T cells], CD4+ or T₄ [helper T cells], CD8+ or T₈ [suppressor T cells], CD20+ [B cells], the CD4-CD8 or T₄-T₈ ratio) and the total lymphocyte count (TLC) showed no significant group differences. Smoking was significantly associated with increases in most cell counts, but not with the CD4-CD8 ratio and CD20+ cells, whereas increasing age was significantly associated with decreasing TLC and CD8+ cells.

Functional studies of T and B cells via reaction to antigenic (tetanus toxoid) or mitogen (phytohemagglutinin [PHA], concanavalin A, and pokeweed) stimulation showed no group differences. Similarly, unadjusted and adjusted mean values of the four assays were not significantly different between groups.

In summary, neither immunologic function nor cell marker studies showed significant impairment in the Ranch Hand group, nor did they show patterns supportive of an herbicide effect. Smoking was associated with a significant increase in the marker cells CD2+ (T cells), CD3+ (T cells), CD4+ (helper T cells), and CD8+ (suppressor T cells), and in the TLC, with a concomitant increase in lymphocytic response to pokeweed mitogen (PWM).

17.1.2.2 1985 Follow-up Summary Results

The 1985 AFHS physical examination placed more emphasis on the immunologic assessment than did the 1982 baseline examination profile. Immunologic competence was measured by cell surface marker (phenotypic) studies and cell stimulation studies on 47 percent of the study population, and by a series of four skin test antigens in 76 percent of the participants to assess the delayed hypersensitivity response.

Surface marker studies were conducted for CD2+ cells (T cells), CD4+ cells (T cells), CD8+ cells (suppressor T cells), CD20+ (B cells), CD14+ cells (monocytes), and HLA-DR cells. The ratio of CD4 to CD8 cells also was included in the analysis. Because of inherent significant day-to-day and batch-to-batch variation, all results (including functional stimulation studies) were adjusted for blood-draw day. Statistical testing of the seven phenotypic cell markers did not reveal any significant group differences, either unadjusted or adjusted, for the covariates of age, race, occupation, current smoking, lifetime smoking history, current alcohol use, or lifetime alcohol use. Similarly, none of the unadjusted or adjusted analyses of the functional stimulation studies (for PHA, PWM, or mixed lymphocyte culture [MLC]) showed any statistically significant group differences. Overall, no pattern was identified to suggest an adverse health effect in any subgroup of either the Ranch Hands or Comparisons.

The effects of age, race, smoking, and alcohol use affected most variables in the phenotypic and stimulation studies. Consistently decreasing values of all cell markers and stimulated cells were associated with increasing age, whereas increased levels of smoking usually were associated with increases in the values of those variables. Blacks had consistently higher stimulated cell counts than non-Blacks, but this effect was not observed for counts of T cells, B cells, or HLA-DR cells. Enlisted personnel generally had higher cell surface marker counts than officers.

The delayed hypersensitivity response was assessed by the skin test antigens of mumps, *Candida albicans*, Trichophyton, and staph-phage lysate. The 48-hour measurements of skin induration and erythema for the four tests showed marked inter-reader variation. Consequently, all skin test data were declared invalid and were not used in the assessment of group differences. The skin test reading problems led to the use of additional clinical quality control procedures for the 1987 follow-up examination.

In conclusion, no significant group differences were found for the comprehensive cell surface marker or functional stimulation studies. The effects of age, smoking, and alcohol use were observed in these immunologic tests.

17.1.2.3 1987 Follow-up Study Summary Results

For the assessment of the 1987 immunologic examination data, results from a composite skin reaction test were evaluated. Various laboratory examination measurements from cell surface marker studies, three groups of functional stimulation tests, and quantitative immunoglobulins also were analyzed. Ranch Hands had a higher frequency of individuals with possibly abnormal reactions on skin testing than Comparisons. The unadjusted analyses of the laboratory examination data indicated no significant group difference between Ranch Hands and Comparisons. For the adjusted analyses of the natural killer assay measurements with and without Interleukin 2 (IL-2), significant interactions between group and race were present. The clinical meaning of these findings was not apparent and did not point to any known clinical endpoints.

17.1.2.4 Serum Dioxin Analysis of 1987 Follow-up Study Summary Results

In general, the composite skin test diagnosis results were not associated with serum dioxin levels. The Ranch Hand analyses using initial dioxin and the analyses using current dioxin and time since duty in Southeast Asia (SEA) generally displayed nonsignificant decreased risks. For the analyses contrasting Ranch Hands with unknown, low, and high current dioxin to Comparisons with background current dioxin levels, the risks were increased but nonsignificant.

For the most part, the cell surface marker variables and TLC did not display significant associations with serum dioxin. The longitudinal analyses of the CD4-CD8 ratio did not consistently show significant differences in the 1987 ratio relative to the 1985 measurement of the ratio.

For the analyses of PHA net responses, significant or marginally significant positive associations with initial dioxin were found. For the analyses involving current dioxin and time since duty in SEA, the maximum PHA net response also displayed some significant or marginally significant positive associations. Depressed immune function would be expected to demonstrate lower PHA net response.

For unstimulated MLC and MLC net response, the three statistical analysis approaches generally displayed nonsignificant associations with serum dioxin. For the analysis involving Ranch Hands in the high current dioxin category and Comparisons in the background current dioxin category, Ranch Hands had a significantly higher unstimulated MLC mean. The analyses of the natural killer cell variables generally were nonsignificant.

Significant positive associations generally were found between IgA and initial dioxin. The analyses for IgA, IgG, and IgM using current dioxin and time since duty in SEA were, for the most part, nonsignificant. For the three immunoglobulins, the overall contrasts of Ranch Hands in the unknown, low, and high current dioxin categories versus Comparisons in the background current dioxin category generally were significant or marginally significant. For IgA and IgG, the contrasts of Ranch Hands in the unknown current dioxin category versus Comparisons in the background current dioxin category were significant with Ranch Hands having lower immunoglobulin averages. For IgM, the contrasts of Ranch Hands in the low current dioxin category versus Comparisons in the background current dioxin category were marginally significant with Ranch Hands again having lower averages. Ranch Hands in the high dioxin category were not significantly different from Comparisons.

The indices of immune responses analyzed in the 1987 examination provided a comprehensive reflection of in vivo and in vitro immune function in the study population. No clinically meaningful indicators reflecting a relation between the current body burden of dioxin or the extrapolated initial exposure and immune function were found. Increased IgA levels may have represented a chronic inflammatory response to dioxin exposure. Elevated erythrocyte sedimentation rates (as discussed in the general health assessment) and increased white blood cell and platelet counts (as discussed in the hematologic

assessment) were other examples of indicators that may have represented a chronic inflammatory response to dioxin exposure.

17.1.2.5 1992 Follow-up Study Summary Results

In general, the composite skin test diagnosis results did not differ significantly between Ranch Hands and Comparisons and were not positively associated with initial or current dioxin levels. For the most part, the cell surface marker variables and total lymphocyte count did not display significant associations with serum dioxin. The longitudinal analyses of the CD4-CD8 ratio did not consistently show significant differences between the 1992 ratio relative to the 1985 measurement of the ratio.

Marginally significant positive associations were found between IgA and initial dioxin. A negative association would be expected in immunologic deficiency, but the increased IgA levels could represent a chronic inflammatory response to dioxin exposure and thus suggested long-term evaluation.

The prevalence of some lupus panel antibodies, such as the MSK smooth muscle antibody and the rheumatoid factor, decreased as dioxin exposure increased. This finding was inconsistent with a harmful effect from dioxin. The presence of lupus panel antibodies generally was considered abnormal. A smaller prevalence of the lupus panel antibodies was found in this study than would be expected in the general population. The presence of a smaller prevalence of abnormalities than expected also may have been regarded as an abnormal finding, suggesting a possible early immune alteration.

17.1.3 Parameters for the 1997 Immunologic Assessment

17.1.3.1 Dependent Variables

Table 17-1 presents the immunologic parameters evaluated and describes their medical importance. The absolute lymphocyte and immunoglobulin studies and lupus panel tests were examined for all participants, whereas the cell surface marker studies were carried out on a random sample of approximately 40 percent of the participants because of the complexity of the assay and the expense of the tests.

Table 17-1. Medical Significance of the Immunologic Data

| Immunologic Measure | Rationale of the Measurement | Disease/Syndrome/Condition Endpoint |
|--|---|--|
| <u>Cell Surface Marker Studies</u> | | |
| CD3+ | Pan-T cell marker (similar to CD2 in previous AFHS examinations). Measures all mature T cells (includes CD4, CD8, etc.). Generally 70% or more of peripheral blood lymphocytes are CD3 positive. | Decrease in absolute number of T cells indicates immunodeficiency. May occur because of direct effects of malignancy (e.g., lymphoma), acquired immune deficiency syndrome (AIDS), or chemotherapy. Increase may occur in lymphoproliferative disorders or in some infections. |
| CD4+ | Measures T cells that exhibit helper/inducer phenotype. CD4 cells initiate an immune response to processed antigens. | Markedly decreased in people with AIDS because of human immunodeficiency virus (HIV) infection of CD4+ cells; increased in autoimmune diseases. |
| CD8+ | Measures T cells that exhibit suppressor and cytotoxic functions. Responsible for appropriate down regulation of an immune response after antigen has been cleared. | Variable in autoimmune diseases; increased in some viral illnesses and immunodeficiencies. |
| CD20+ (B1) | Measures peripheral blood B cells; no reaction with T cells, granulocytes, or monocytes. | Decreased result in humoral immune deficiency with impaired production of antibodies; increased in lymphoproliferative disorders. |
| Double Labeled Cells (cells that express both markers) | | |
| CD3+CD4+ | Helper T cells and excludes monocytes but more specific than CD4. | Same as CD4. |
| CD16+56+ (CD3-) | Normally these markers do not occur on the same cells. Measures natural killer (NK) cells that can lyse foreign cells independent of antibody or prior contact with the target. CD16 is an IgG receptor that appears on NK cells and neutrophils; CD56 is more restricted to NK cells; joint use of CD16 and CD56 enhances enumeration of NK cells. | NK cells are thought to attack neoplasms and naturally prevent growth of cancers. |
| <u>Absolute Lymphocytes</u> | | |
| | Measures absolute number of total lymphocytes circulating in peripheral blood. Major immune mechanism against fungi and viruses. | Decreased in immunodeficiency; increased in lymphoproliferative disorders. |

Table 17-1. Medical Significance of the Immunologic Data (Continued)

| Immunologic Measure | Rationale of the Measurement | Disease/Syndrome/Condition Endpoint |
|--|--|--|
| <u>Immunoglobulins</u> | | |
| IgG IgA IgM | Each measures ability of specific B cell subgroup to secrete specific antibody class of molecules. Antibodies normally rise in response to infections or immunizations with bacteria, fungi, and viruses. Major immune mechanism against bacteria. | Increased in hyperglobulinemia or myeloma (monoclonal). Decreased in selective or total B cell immunodeficiency. Polyclonal increases in chronic inflammation and liver disease (cirrhosis). |
| <u>Lupus Panel</u> | | |
| The test composition of this profile was chosen to include the most frequently encountered autoantibodies. Presence of autoantibodies may indicate specific autoimmune diseases, especially if multiple autoantibodies are present. The individually named autoantibodies (excluding ANA and B cell clones) are associated with specific diseases. Any of these tests may also turn positive as a participant's immune system ages or otherwise is dysregulated. | | |
| Antinuclear Antibody (ANA) Test | Screening assay (performed with monolayers of HEP-2) for many clinically meaningful autoantibodies that occur in systemic rheumatologic diseases. | Positive result suggests possible rheumatologic disease; likelihood increases with number of different positive autoantibodies. |
| ANA Thyroid Microsomal Antibody | Measures autoantibodies against thyroid microsomal antigen. | Present in autoimmune thyroiditis. |
| MSK Smooth Muscle Antibody | MSK indicates the tissues used in the assay (mouse stomach kidney); measures autoantibodies against actin in smooth muscle. | Present in autoimmune liver diseases, especially chronic active hepatitis. |
| MSK Mitochondrial Antibody | Measures autoantibodies against mitochondrial antigens. | Present in autoimmune liver diseases, especially primary biliary cirrhosis. |
| MSK Parietal Antibody | Measures autoantibodies against parietal cells of the stomach that make intrinsic factor for the absorption of vitamin B ₁₂ . | Present in pernicious anemia (failure to absorb vitamin B ₁₂). |
| Rheumatoid Factor | Autoantibodies reactive with a person's own antibodies. | Present in rheumatoid arthritis; also in some infections, chronic pulmonary diseases, and other inflammatory or autoimmune diseases. |

17.1.3.1.1 Laboratory Examination Data

The results of cell surface marker studies, absolute lymphocytes, quantitative immunoglobulins, and a lupus panel were analyzed. Participants who were taking anti-inflammatory medication (except aspirin and nonsteroidal) or immunosuppressant medication at the time of the 1997 physical examination were excluded from analysis. Participants who had recently received x-ray treatment or chemotherapy for cancer and participants who tested positive for HIV also were excluded from analysis.

17.1.3.1.1.1 Cell Surface Marker (Phenotypic) Studies

Quantification of the different cell populations was carried out with the use of reagent mouse monoclonal antibodies. Cell surface markers were analyzed in the statistical evaluation of the immunologic system. The unit of measurement was cells/mm³. The CD3+CD4+ (helper T cells) double labeled cell surface marker was introduced to the AFHS for the 1997 follow-up examination.

17.1.3.1.1.2 Absolute Lymphocytes

Absolute lymphocytes indicate the density of lymphocytes in the blood. Lymphocytes recognize and destroy bacteria, fungi, viruses, and other foreign bodies. Statistical analyses were performed on absolute lymphocytes, measured in cells/mm³.

Absolute lymphocytes also were analyzed in Chapter 15, Hematology Assessment (Table 15-19). The analysis of absolute lymphocytes in the Hematology Assessment chapter included nonreactive lymphocytes, whereas the analysis in this chapter included nonreactive and reactive lymphocytes. In addition, the analysis in this chapter included age, race, military occupation, current cigarette smoking, lifetime cigarette smoking history, current alcohol use, lifetime alcohol history, and a physical activity index as covariates. The analysis in the Hematology Assessment chapter did not include current alcohol use, lifetime alcohol history, or the physical activity index. The exclusions for analysis in the Hematology Assessment included participants with body temperatures greater than or equal to 100° Fahrenheit and participants testing positive for HIV. The exclusions in this chapter included participants who were taking anti-inflammatory (except aspirin and nonsteroidal) or immunosuppressant medication at the time of the 1997 physical examination. Participants who had recently received x-ray treatment or chemotherapy for cancer and participants who tested positive for HIV also were excluded from analysis in this chapter.

17.1.3.1.1.3 Immunoglobulins

Immunoglobulins measure the ability of a specific B cell subgroup to secrete a specific antibody class of molecules. The antibodies usually rise in response to infections or immunizations with bacteria, fungi, and viruses. Statistical analyses were performed on the immunoglobulins IgA, IgG, and IgM, measured in mg/dl.

17.1.3.1.1.4 Lupus Panel

This group of laboratory tests was configured to detect the most frequent autoantibodies found in both patients and asymptomatic individuals. Autoantibodies are markers for autoimmune diseases, and the lupus panel is considered a screening assay for a wide spectrum of autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus). Occasionally, autoantibodies are detected in asymptomatic persons; this is alternatively explained as evidence for incipient autoimmune disease or a finding of unknown meaning. In any instance, the finding of an autoantibody is not normal and should be

interpreted as an aberration of the immune system. The lupus panel was composed of the following individual tests on serum:

- Antinuclear antibody (ANA) performed on HEP-2 cells
- Mouse stomach kidney (MSK) section stain for the following specific autoantibodies:
 - Smooth muscle
 - Mitochondrial
 - Parietal cell
- Thyroid microsomal antibody
- Rheumatoid factor.

All of the autoantibodies derive from abnormalities of the B cell portion, the part of the immune system that produces immunoglobulins.

Statistical analyses were performed on the ANA, ANA thyroid microsomal antibody, MSK smooth muscle antibody, MSK mitochondrial antibody, MSK parietal cell antibody, and rheumatoid factor, with the response to these tests scored as present or absent.

17.1.3.2 Covariates

Covariates to be used in the immunologic evaluation for adjusted statistical analyses included age, race, military occupation, current alcohol use (drinks/day), lifetime alcohol history (drink-years), current cigarette smoking (cigarettes/day), lifetime cigarette smoking history (pack-years), and exercise history (an index combining both duration and intensity).

Age, race, and military occupation were determined from military records. Lifetime alcohol history was based on information from the 1997 questionnaire and combined with similar information gathered at the 1987 and 1992 follow-up examinations. Each participant was asked about his drinking patterns throughout his lifetime. When a participant's drinking patterns changed, he was asked to describe how his alcohol consumption differed and the duration of time that the drinking pattern lasted. The participant's average daily alcohol consumption was determined for each of the reported drinking pattern periods throughout his lifetime, and an estimate of the corresponding total number of drink-years was derived. One drink-year was the equivalent of drinking 1.5 ounces of an 80-proof alcoholic beverage, one 12-ounce beer, or one 5-ounce glass of wine per day for 1 year. Current alcohol use was defined as the average number of drinks per day during the month prior to completing the questionnaire.

Current cigarette smoking and lifetime cigarette smoking history were based on questionnaire data. For lifetime cigarette smoking history, the respondent's average smoking was estimated over his lifetime based on his responses to the 1997 questionnaire, with 1 pack-year defined as 365 packs of cigarettes smoked during a single year.

A series of questions concerning exercise patterns in the 2 weeks prior to the physical examination were included as part of the 1997 questionnaire. The participants were asked questions on frequency, average duration per frequency, and increase of heart rate or breathing for more than 20 different activities. The answers to these questions were used and combined to determine an index of physical activity incorporating duration and intensity (88, 89), and this covariate was used in adjusted statistical analyses. A participant was classified as active, moderately active, or sedentary based on his responses to the series of questions regarding exercise patterns.

17.1.4 Statistical Methods

Chapter 7, Statistical Methods, describes the basic statistical methods to be used in the immunologic assessment. For the 1985, 1997, and 1992 follow-up studies, large variation was observed from examination group variability. Because of the variation, this covariate generally was incorporated into the unadjusted and the adjusted models of the respective immunologic assessments for the 1985, 1987, and 1992 studies. Plans had been made to use examination group as a covariate in the analysis of the 1997 immunologic data; however, examination group was not significantly associated with immunologic data in the 1997 follow-up study and, consequently, examination group was not used as a covariate in the analyses described in this chapter.

Table 17-2 summarizes the statistical analyses to be performed for the analysis of the immunologic assessment. The first part of this table lists the dependent variables to be analyzed. The second part of the table further describes the covariates to be examined. A covariate was used in its continuous form whenever possible for all adjusted analyses. If the covariate was inherently discrete (e.g., military occupation), or if a categorized form was needed to develop measures of association with the dependent variables, the covariate was categorized as shown in Table 17-2.

Table 17-2. Statistical Analysis for the Immunologic Assessment

Dependent Variables

| Variable (Units) | Data Source | Data Form | Normal Range/ Cutpoints ^a | Covariates ^b | Exclusions ^c | Statistical Analysis and Methods |
|--|-------------|-----------|---|-------------------------|-------------------------|----------------------------------|
| CD3+ Cells (T Cells) (cells/mm ³) | LAB | C | 700–2,400 | (1) | (a) | U:GLM A:GLM |
| CD4+ Cells (Helper T Cells) (cells/mm ³) | LAB | C | 400–1,400 | (1) | (a) | U:GLM A:GLM |
| CD8+ Cells (Suppressor Cells) (cells/mm ³) | LAB | C | 300–900 | (1) | (a) | U:GLM A:GLM |
| CD16+56+ Cells (Natural Killer Cells) (cells/mm ³) | LAB | C | 48–450 | (1) | (a) | U:GLM A:GLM |
| CD20+ Cells (B Cells) (cells/mm ³) | LAB | C | -- | (1) | (a) | U:GLM A:GLM |
| CD3+CD4+ Cells (Helper T Cells) (cells/mm ³) | LAB | C | 400–1,400 | (1) | (a) | U:GLM A:GLM |
| Absolute Lymphocytes (cells/mm ³) | LAB | C | 1,000–4,800 | (1) | (a) | U:GLM A:GLM |
| IgA (mg/dl) | LAB | C | 69–382 | (1) | (a) | U:GLM A:GLM |
| IgG (mg/dl) | LAB | C | 723–1,685 | (1) | (a) | U:GLM A:GLM |
| IgM (mg/dl) | LAB | C | 63–277 | (1) | (a) | U:GLM A:GLM |
| Lupus Panel: ANA Test | LAB | D | Present Absent | (1) | (a) | U:LR A:LR |
| Lupus Panel: ANA Thyroid Microsomal Antibody | LAB | D | Present Absent | (1) | (a) | U:LR A:LR |

Table 17-2. Statistical Analysis for the Immunologic Assessment (Continued)

| Variable (Units) | Data Source | Data Form | Normal Range/Cutpoints ^a | Covariates ^b | Exclusions ^c | Statistical Analysis and Methods |
|---|-------------|-----------|-------------------------------------|-------------------------|-------------------------|----------------------------------|
| Lupus Panel: MSK Smooth Muscle Antibody | LAB | D | Present Absent | (1) | (a) | U:LR A:LR |
| Lupus Panel: MSK Mitochondrial Antibody | LAB | D | Present Absent | (1) | (a) | U:LR,CS A:LR |
| Lupus Panel: MSK Parietal Antibody | LAB | D | Present Absent | (1) | (a) | U:LR A:LR |
| Lupus Panel: Rheumatoid Factor | LAB | D | Present Absent | (1) | (a) | U:LR A:LR |

^a Normal ranges are presented for cell surface markers, absolute lymphocytes, and immunoglobulins for reference purposes. Statistical analyses were done only on the continuous form of these dependent variables.

^b Covariates:

(1): age, race, military occupation, current cigarette smoking, lifetime cigarette smoking history, current alcohol use, lifetime alcohol history, physical activity index.

^c Exclusions:

(a): participants taking anti-inflammatory (except aspirin and nonsteroidal) or immunosuppression medications, participants testing positive for HIV, participants who recently received x-ray treatment or chemotherapy for cancer.

Covariates

| Variable (Units) | Data Source | Data Form | Cutpoints |
|---|-------------|-----------|--|
| Age (years) | MIL | D/C | Born≥1942 Born<1942 |
| Race | MIL | D | Black Non-Black |
| Occupation | MIL | D | Officer Enlisted Flyer Enlisted Groundcrew |
| Current Cigarette Smoking (cigarettes/day) | Q-SR | D/C | 0-Never 0-Former >0-20 >20 |
| Lifetime Cigarette Smoking History (pack-years) | Q-SR | D/C | 0 >0-10 >10 |
| Current Alcohol Use (drinks/day) | Q-SR | D/C | 0-1 >1-4 >4 |

Table 17-2. Statistical Analysis for the Immunologic Assessment (Continued)

| Variable (Units) | Data Source | Data Form | Cutpoints |
|--|-------------|-----------|--|
| Lifetime Alcohol History (drink-years) | Q-SR | D/C | 0 >0-40 >40 |
| Physical Activity Index (kcal/kg/day) | Q-SR | D | Sedentary: <1.45 Moderate: 1.45-<2.95 Very Active: ≥2.95 |

Abbreviations

Data Source: LAB: 1997 laboratory results
MIL: Air Force military records
Q-SR: Health questionnaires (self-reported)

Data Form: D: Discrete analysis only
C: Continuous analysis only
D/C: Appropriate form for analysis (either discrete or continuous) for covariates

Statistical Analysis: U: Unadjusted analysis
A: Adjusted analysis

Statistical Methods: CS: Chi-square contingency table analysis (continuity-adjusted)
GLM: General linear models analysis
LR: Logistic regression analysis

Table 17-3 provides a summary of participants with missing dependent variable and covariate data. In addition, the number of participants excluded is given. Because approximately 40 percent of the participants were assayed for cell surface markers, Table 17-3 is divided into two parts: (1) a summary for cell surface markers and (2) a summary for absolute lymphocytes, immunoglobulins, and the lupus panel.

Table 17-3. Number of Participants Excluded or with Missing Data for the Immunologic Assessment

| Variable | Variable Use | Group | | Dioxin (Ranch Hands Only) | | Categorized Dioxin | |
|------------------------------------|--------------|------------|------------|---------------------------|------|--------------------|------------|
| | | Ranch Hand | Comparison | Initial | 1987 | Ranch Hand | Comparison |
| Cell Surface Markers | | | | | | | |
| CD20+ Cells (B Cells) | DEP | 1 | 0 | 1 | 1 | 1 | 0 |
| Current Cigarette Smoking | COV | 1 | 0 | 0 | 1 | 1 | 0 |
| Lifetime Cigarette Smoking History | COV | 2 | 1 | 1 | 2 | 2 | 1 |
| Current Alcohol Use | COV | 1 | 0 | 0 | 1 | 1 | 0 |
| Lifetime Alcohol History | COV | 2 | 0 | 1 | 2 | 2 | 0 |
| Physical Activity Index | COV | 3 | 3 | 1 | 3 | 3 | 3 |

Table 17-3. Number of Participants with Missing Data for the Immunologic Assessment (Continued)

| | | | | | | | |
|---|-----|----|----|----|----|----|----|
| Taking Anti-Inflammatory or Immunosuppressant Medications | EXC | 12 | 12 | 8 | 12 | 12 | 11 |
| Recent X-ray Treatment or Chemotherapy for Cancer | EXC | 10 | 8 | 9 | 10 | 10 | 7 |
| HIV Positive | EXC | 0 | 2 | 0 | 0 | 0 | 2 |
| Absolute Lymphocytes, Immunoglobulins, and Lupus Panel | | | | | | | |
| Current Cigarette Smoking | COV | 1 | 0 | 0 | 1 | 1 | 0 |
| Lifetime Cigarette Smoking History | COV | 2 | 1 | 1 | 2 | 2 | 1 |
| Current Alcohol Use | COV | 1 | 0 | 0 | 1 | 1 | 0 |
| Lifetime Alcohol History | COV | 6 | 2 | 3 | 6 | 6 | 1 |
| Physical Activity Index | COV | 6 | 8 | 2 | 6 | 6 | 8 |
| Taking Anti-Inflammatory or Immunosuppressant Medications | EXC | 23 | 34 | 14 | 23 | 23 | 32 |
| Recent X-ray Treatment or Chemotherapy for Cancer | EXC | 14 | 17 | 12 | 13 | 13 | 16 |
| HIV Positive | EXC | 3 | 2 | 3 | 3 | 3 | 2 |

Note: DEP = Dependent variable.
COV = Covariate.
EXC = Exclusion.

Cell Surface Markers:

341 Ranch Hands and 477 Comparisons.
192 Ranch Hands for initial dioxin; 339 Ranch Hands for 1987 dioxin.
339 Ranch Hands and 460 Comparisons for categorized dioxin.

Absolute Lymphocytes, Immunoglobulins, and Lupus Panel:

870 Ranch Hands and 1,251 Comparisons.
482 Ranch Hands for initial dioxin; 863 Ranch Hands for 1987 dioxin.
863 Ranch Hands and 1,213 Comparisons for categorized dioxin.

17.2 RESULTS

17.2.1 Dependent Variable-Covariate Associations

Tests of association between the immunologic dependent variables and each of the covariates given in Table 17-2 were conducted. The results are presented in Appendix Table F-9. These associations are pairwise between the dependent variable and the covariate and are not adjusted for any other covariates. Participants taking anti-inflammatory medications, taking immunosuppression medication, testing positive for HIV, or who have recently received x-ray treatment or chemotherapy for cancer were excluded from all analyses.

The analysis of CD3+ cells (T cells) revealed a significant association with age ($p=0.006$), indicating a decrease in the CD3+ cell count as age increased. A marginally significant association was found

between race and CD3+ cell count ($p=0.095$). Blacks displayed a higher mean CD3+ cell count (mean=1,363.1 cells/mm³) than non-Blacks (mean=1,239.6 cells/mm³). Analyses also revealed significant associations between CD3+ cell count and current cigarette smoking ($p<0.001$) and between CD3+ cell count and the physical activity index ($p<0.001$). CD3+ cell count increased as the number of cigarettes per day increased and as the activity level decreased.

Tests of association for CD4+ cell (helper T cell) count were significant for age ($p<0.001$), race ($p=0.023$), current cigarette smoking ($p<0.001$), and the physical activity index ($p=0.001$). A marginally significant association was found with lifetime cigarette smoking history ($p=0.053$). The CD4+ cell count decreased with age, and the CD4+ cell count mean was higher for Blacks (mean=958.7 cells/mm³) than for non-Blacks (mean=844.4 cells/mm³). As the number of cigarettes per day increased, the CD4+ cell count increased. Participants with the lowest activity level displayed the highest average CD4+ cell counts (mean=889.2 cells/mm³); the cell count increased as the number of cigarette pack-years increased.

Significant associations with the CD8+ cell (suppressor T cell) count were found for the current cigarette smoking ($p<0.001$) and the physical activity index covariates ($p=0.005$). The CD8+ cell count increased as the number of cigarettes smoked per day increased. The mean CD8+ cell count was highest among those participants classified as sedentary (mean=608.3 cells/mm³). Participants classified as active displayed the next highest CD8+ cell count mean (mean=548.3 cells/mm³), followed by those with a moderately active index (mean=539.1 cells/mm³).

Covariate association tests conducted for the CD16+56+ cell (natural killer cell) count analysis resulted in significant findings for age ($p=0.005$) and current cigarette smoking ($p<0.001$). The CD16+56+ cell count increased as age increased and as the number of cigarettes smoked per day decreased.

Significant covariate associations with the CD20+ cell (B cell) count were found for age ($p<0.001$), race ($p=0.007$), occupation ($p=0.002$), current cigarette smoking ($p<0.001$), current alcohol use ($p=0.007$), and the physical activity index ($p=0.017$). The CD20+ cell count decreased with age, and the CD20+ cell count mean was higher for Blacks (mean=232.9 cells/mm³) than for non-Blacks (mean=182.2 cells/mm³). Enlisted groundcrew showed the highest average CD20+ cell count (mean=200.9 cells/mm³), followed by enlisted flyers (mean=178.8 cells/mm³) and officers (mean=170.8 cells/mm³). The CD20+ cell count increased as the number of cigarettes smoked per day increased and as the number of drinks per day decreased. The CD20+ cell count increased as the physical activity level decreased.

Tests of covariate associations with the CD3+CD4+ cell (helper T cell) count were significant for age ($p<0.001$), current cigarette smoking ($p<0.001$), lifetime cigarette smoking history ($p=0.032$), and the physical activity index ($p=0.001$), and marginally significant for race ($p=0.061$). The CD3+CD4+ cell count decreased with age. The mean CD3+CD4+ cell count was higher for Blacks (mean=860.6 cells/mm³) than for non-Blacks (mean=770.2 cells/mm³). The CD3+CD4+ cell count increased as current and lifetime cigarette smoking increased. Participants in the sedentary category of the physical activity index showed the highest CD3+CD4+ cell count (mean=814.3 cells/mm³).

Association tests for absolute lymphocytes revealed significant findings for age ($p<0.001$), occupation ($p<0.001$), current cigarette smoking ($p<0.001$), lifetime cigarette smoking history ($p<0.001$), and the physical activity index ($p<0.001$). The association between absolute lymphocytes and race was marginally significant ($p=0.070$). Absolute lymphocytes decreased with age and increased as cigarette smoking increased. Enlisted groundcrew had the highest average absolute lymphocyte count (mean=1,845.8 cells/mm³), followed by enlisted flyers (mean=1,788.5 cells/mm³), then officers (mean=1,703.3 cells/mm³). Blacks displayed a higher mean absolute lymphocyte count (mean=1,879.4 cells/mm³) than did non-Blacks (mean=1,772.9 cells/mm³). The least active participants displayed the

highest average absolute lymphocyte count (mean=1,831.0 cells/mm³), compared to those who were moderately active (mean=1,722.7 cells/mm³) and active (mean=1,719.7 cells/mm³).

The covariate association analysis for IgA displayed significant findings for age (p=0.012), occupation (p=0.030), and current alcohol use (p=0.032). Marginally significant findings resulted for lifetime alcohol use (p=0.086) and the physical activity index (p=0.088). IgA levels increased with age, current alcohol use, and lifetime alcohol use. Average IgA levels were highest among enlisted groundcrew (mean=238.7 mg/dl), followed by enlisted flyers (mean=237.3 mg/dl), then officers (mean=225.0 mg/dl). Participants with the lowest activity levels displayed the highest mean IgA levels.

Analysis of IgG revealed significant associations with race (p<0.001), occupation (p=0.019), current cigarette smoking (p<0.001), lifetime cigarette smoking (p<0.001), current alcohol use (p<0.001), and lifetime alcohol history (p=0.007). Blacks exhibited a higher average IgG level (mean=1,266.8 mg/dl) than non-Blacks (mean=1,029.2 mg/dl). Enlisted groundcrew exhibited the highest average IgG level (mean=1,058.6 mg/dl) among the occupational strata, followed by enlisted flyers (mean=1,036.8 mg/dl), then officers (mean=1,026.7 mg/dl). IgA levels decreased as current and lifetime cigarette smoking increased and as current and lifetime alcohol use increased.

The covariate analysis of IgM levels revealed significant associations with age (p=0.005), race (p=0.004), and current alcohol use (p=0.010). IgM levels decreased as age increased. Non-Blacks displayed higher average levels of IgM (mean=98.4 mg/dl) as compared to Blacks (mean=85.4 mg/dl). IgM levels increased as the current alcohol use increased.

Tests of association between covariates and ANA revealed a marginally significant relation with age (p=0.098) and significant relations with current cigarette smoking (p=0.001) and lifetime cigarette smoking history (p=0.033). The presence of the ANA was higher among older participants (53.7%) than among younger participants (49.9%). Cigarette smokers who smoke at most 20 cigarettes per day and those with more than 10 pack-years exhibited the greatest percentages of the ANA present (63.2% and 55.1%, respectively).

A marginally significant association between thyroid microsomal antibody and the physical activity index was observed (p=0.061). The highest percentage of participants with the thyroid microsomal antibody present was found in the moderately active category (4.3%), followed by those classified as sedentary (2.9%), then those classified as active (1.7%).

Significant covariate associations for the MSK smooth muscle antibody test included race (p=0.018) and current cigarette smoking (p=0.037). A marginally significant association with the physical activity index was observed (p=0.085). Blacks exhibited a higher presence of the MSK smooth muscle antibody than non-Blacks (19.2% vs. 11.7%, respectively). Cigarette smokers who smoked at most 20 cigarettes per day displayed the highest presence of the smooth muscle antibody (17.2%). Participants categorized as moderately active exhibited the highest presence of the smooth muscle antibody (13.5%), followed by those who were classified as sedentary (12.9%), then those who were active (9.5%).

Tests of covariate association for the MSK mitochondrial antibody revealed a marginally significant association with occupation (p=0.060). Officers had the highest prevalence of the antibody (0.6%), followed by enlisted flyers (0.3%), then enlisted groundcrew (0.0%).

The MSK parietal antibody test displayed a significant covariate association with race (p=0.001). For Blacks, 10.4 percent exhibited the presence of the antibody, as compared to 3.9 percent of non-Blacks.

Association tests for the rheumatoid factor showed age to be marginally significant ($p=0.064$) and occupation and lifetime cigarette smoking history to be significant ($p=0.038$ and $p=0.006$, respectively). The presence of the rheumatoid factor was higher among the older participants (12.2%), compared to a prevalence of 9.5 percent for the younger participants. Enlisted flyers displayed the highest prevalence of a positive rheumatoid factor (13.1%), followed by officers (12.3%), then enlisted groundcrew (9.0%). The heaviest lifetime smokers (in terms of pack-years) showed the highest presence of the rheumatoid factor (12.8%), followed by nonsmokers (11.6%), then moderate lifetime smokers (7.4%).

17.2.2 Exposure Analysis

The following section presents results of the statistical analyses of the dependent variables shown in Table 17-2. Dependent variables were derived from the results of the laboratory portion of the 1997 follow-up examination.

Four models were examined for each dependent variable given in Table 17-2. The analyses of these models are presented below. Further details on dioxin and the modeling strategy are found in Chapters 2 and 7, respectively. These analyses were performed both unadjusted and adjusted for relevant covariates. Model 1 examined the relation between the dependent variable and group (i.e., Ranch Hand or Comparison). In this model, exposure was defined as “yes” for Ranch Hands and “no” for Comparisons without regard to the magnitude of the exposure. As an attempt to quantify exposure, three contrasts of Ranch Hands and Comparisons were performed along with the overall Ranch Hand versus Comparison contrast. These three contrasts compared Ranch Hands and Comparisons within each occupational category (i.e., officers, enlisted flyers, and enlisted groundcrew). As described in previous reports and Table 2-8, the average levels of exposure to dioxin were highest for enlisted groundcrew, followed by enlisted flyers, then officers.

Model 2 explored the relation between the dependent variable and an extrapolated initial dioxin measure for Ranch Hands who had a 1987 dioxin measurement greater than 10 ppt. If a participant did not have a 1987 dioxin level, the 1992 level was used to estimate the initial dioxin level. If a participant did not have a 1987 or a 1992 dioxin level, the 1997 level was used to estimate the initial dioxin level. A statistical adjustment for the percentage of body fat at the time of the participant’s blood measurement of dioxin was included in this model to account for body-fat-related differences in elimination rate (90).

Model 3 divided the Ranch Hands examined in Model 2 into two categories based on their initial dioxin measures. These two categories are referred to as “low Ranch Hand” and “high Ranch Hand.” Two additional categories, Ranch Hands with 1987 serum dioxin levels at or below 10 ppt and Comparisons with 1987 serum dioxin levels at or below 10 ppt, were formed and included in the model. Ranch Hands with 1987 serum dioxin levels at or below 10 ppt are referred to as the “background Ranch Hand” category. Dioxin levels in 1992 were used if the 1987 level was not available and dioxin levels in 1997 were used if the 1987 and 1992 levels were not available. These four categories—Comparison, background Ranch Hands, low Ranch Hands, and high Ranch Hands—were used in Model 3 analyses. The relation between the dependent variable in each of the three Ranch Hand categories and the dependent variable in the Comparison category was examined. A fourth contrast, exploring the relation of the dependent variable in the combined low and high Ranch Hand categories relative to Comparisons, also was conducted. This combination is referred to in the tables as the “low plus high Ranch Hand” category. As in Model 2, a statistical adjustment for the percentage of body fat at the time of the participant’s blood measurement of dioxin was included in this model.

Model 4 examined the relation between the dependent variable and 1987 lipid-adjusted dioxin levels in all Ranch Hands with a dioxin measurement. If a participant did not have a 1987 dioxin measurement, the

1992 measurement was used to determine the dioxin level. If a participant did not have a 1987 or a 1992 dioxin measurement, the 1997 measurement was used to determine the dioxin level.

17.2.2.1 *Laboratory Variables*

17.2.2.1.1 *CD3+ Cells (T Cells)*

The Model 1 adjusted analysis of CD3+ cells revealed a marginally significant difference in means between Ranch Hands and Comparisons within the enlisted groundcrew stratum (Table 17-4(b): $p=0.073$, difference of adjusted means= -91.7 cells/mm³). The mean CD3+ cell count was higher for Comparisons than for Ranch Hands. All other Model 1 contrasts, as well as the Model 2 and Model 3 analyses, were nonsignificant (Table 17-4(a-f): $p>0.11$ for all analyses).

Results from the Model 4 unadjusted analysis of CD3+ cells were nonsignificant (Table 17-4(g): $p=0.316$). After adjustment for covariates, a significant and positive association between the 1987 dioxin levels and CD3+ cell count was observed (Table 17-4(h): $p=0.046$, adjusted slope= 0.035). CD3+ cell counts increased as 1987 dioxin levels increased.

Table 17-4. Analysis of CD3+ Cells (T Cells) (cells/mm³)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|------------|-------------------------|---|----------------------------|
| Occupational Category | Group | n | Mean^a | Difference of Means (95% C.I.)^b | p-Value^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>319</i> | <i>1,231.0</i> | <i>-26.7 --</i> | <i>0.431</i> |
| | <i>Comparison</i> | <i>455</i> | <i>1,257.7</i> | | |
| Officer | Ranch Hand | 135 | 1,230.0 | 39.8 -- | 0.449 |
| | Comparison | 164 | 1,190.2 | | |
| Enlisted Flyer | Ranch Hand | 56 | 1,197.2 | -89.6 -- | 0.270 |
| | Comparison | 78 | 1,286.8 | | |
| Enlisted Groundcrew | Ranch Hand | 128 | 1,247.1 | -54.2 -- | 0.308 |
| | Comparison | 213 | 1,301.3 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Table 17-4. Analysis of CD3+ Cells (T Cells) (cells/mm³) (Continued)

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|------------|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>316</i> | <i>1,245.2</i> | -38.5 -- | <i>0.255</i> |
| | <i>Comparison</i> | <i>451</i> | <i>1,283.7</i> | | |
| Officer | Ranch Hand | 134 | 1,313.3 | 46.8 -- | 0.392 |
| | Comparison | 162 | 1,266.5 | | |
| Enlisted Flyer | Ranch Hand | 56 | 1,201.6 | -96.8 -- | 0.224 |
| | Comparison | 77 | 1,298.4 | | |
| Enlisted Groundcrew | Ranch Hand | 126 | 1,205.6 | -91.7 -- | 0.073 |
| | Comparison | 212 | 1,297.3 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | Analysis Results for Log₂ (Initial Dioxin)^b | | |
|---|----------|-------------------------|-------------------------------|--|---------------------------------------|----------------|
| Initial Dioxin Category Summary Statistics | | | | R² | Slope (Std. Error)^c | p-Value |
| Initial Dioxin | n | Mean^a | Adj. Mean^{ab} | | | |
| Low | 52 | 1,163.0 | 1,166.8 | 0.013 | 0.023 (0.023) | 0.317 |
| Medium | 61 | 1,288.6 | 1,285.9 | | | |
| High | 62 | 1,263.7 | 1,262.9 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of CD3+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | Analysis Results for Log₂ (Initial Dioxin) | | |
|---|----------|------------------------------|--|--|--|----------------|
| Initial Dioxin Category Summary Statistics | | | | R² | Adj. Slope (Std. Error)^b | p-Value |
| Initial Dioxin | n | Adj. Mean^a | | | | |
| Low | 52 | 1,237.6 | | 0.132 | 0.042 (0.027) | 0.113 |
| Medium | 60 | 1,358.6 | | | | |
| High | 62 | 1,388.6 | | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD3+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-4. Analysis of CD3+ Cells (T Cells) (cells/mm³) (Continued)

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|----------|-------------------------|-------------------------------|---|----------------------------|
| Dioxin Category | n | Mean^a | Adj. Mean^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.)^c | p-Value^d |
| Comparison | 440 | 1,252.8 | 1,252.1 | | |
| Background RH | 142 | 1,210.4 | 1,220.8 | -31.3 -- | 0.490 |
| Low RH | 84 | 1,230.2 | 1,225.9 | -26.2 -- | 0.636 |
| High RH | 91 | 1,251.6 | 1,242.7 | -9.4 -- | 0.862 |
| Low plus High RH | 175 | 1,241.3 | 1,234.6 | -17.5 -- | 0.676 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | |
|---|----------|------------------------------|---|----------------------------|
| Dioxin Category | n | Adj. Mean^a | Difference of Adj. Mean vs. Comparisons (95% C.I.)^b | p-Value^c |
| Comparison | 436 | 1,284.8 | | |
| Background RH | 140 | 1,237.1 | -47.7 -- | 0.308 |
| Low RH | 83 | 1,272.3 | -12.5 -- | 0.823 |
| High RH | 91 | 1,239.3 | -45.5 -- | 0.403 |
| Low plus High RH | 174 | 1,254.9 | -29.9 -- | 0.474 |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 17-4. Analysis of CD3+ Cells (T Cells) (cells/mm³) (Continued)

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | | |
|--|----------|-------------------------|--|---------------------------------------|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin +1) | | |
| 1987 Dioxin | n | Mean^a | R² | Slope (Std. Error)^b | p-Value |
| Low | 110 | 1,196.2 | 0.003 | 0.015 (0.015) | 0.316 |
| Medium | 100 | 1,216.1 | | | |
| High | 107 | 1,271.3 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD3+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|----------|------------------------------|---|--|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean^a | R² | Adjusted Slope (Std. Error)^b | p-Value |
| Low | 108 | 1,149.8 | 0.088 | 0.035 (0.018) | 0.046 |
| Medium | 100 | 1,220.5 | | | |
| High | 106 | 1,286.6 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD3+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

17.2.2.1.2 CD4+ Cells (Helper T Cells)

The unadjusted and adjusted analyses of CD4+ cells in Models 1, 2, and 3, as well as the unadjusted analysis in Model 4, were nonsignificant (Table 17-5(a–g): $p > 0.11$ for all analyses). The adjusted analysis of Model 4 revealed a significant and positive association between the 1987 dioxin levels and the CD4+ cell count (Table 17-5(h): $p = 0.033$, adjusted slope = 0.038). CD4+ cell counts increased as 1987 dioxin increased.

Table 17-5. Analysis of CD4+ Cells (Helper T Cells) (cells/mm³)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|------------|-------------------|---|----------------------|
| Occupational Category | Group | n | Mean ^a | Difference of Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>319</i> | <i>842.0</i> | <i>-15.0 --</i> | <i>0.511</i> |
| | <i>Comparison</i> | <i>455</i> | <i>857.0</i> | | |
| Officer | Ranch Hand | 135 | 838.0 | 13.3 -- | 0.708 |
| | Comparison | 164 | 824.7 | | |
| Enlisted Flyer | Ranch Hand | 56 | 808.4 | -61.8 -- | 0.254 |
| | Comparison | 78 | 870.2 | | |
| Enlisted Groundcrew | Ranch Hand | 128 | 861.4 | -16.5 -- | 0.646 |
| | Comparison | 213 | 877.9 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|------------|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>316</i> | <i>871.6</i> | <i>-22.4 --</i> | <i>0.333</i> |
| | <i>Comparison</i> | <i>451</i> | <i>894.0</i> | | |
| Officer | Ranch Hand | 134 | 926.9 | 20.0 -- | 0.601 |
| | Comparison | 162 | 906.9 | | |
| Enlisted Flyer | Ranch Hand | 56 | 835.6 | -61.0 -- | 0.261 |
| | Comparison | 77 | 896.5 | | |
| Enlisted Groundcrew | Ranch Hand | 126 | 842.4 | -44.0 -- | 0.205 |
| | Comparison | 212 | 886.4 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | | | |
|---|----|-------------------|-------------------------|---|---------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | | Analysis Results for Log ₂ (Initial Dioxin) ^b | | |
| Initial Dioxin | n | Mean ^a | Adj. Mean ^{ab} | R ² | Slope (Std. Error) ^c | p-Value |
| Low | 52 | 804.2 | 807.5 | 0.018 | 0.027 (0.023) | 0.254 |
| Medium | 61 | 883.0 | 880.6 | | | |
| High | 62 | 869.6 | 868.8 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of CD4+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-5. Analysis of CD4+ Cells (Helper T Cells) (cells/mm³) (Continued)

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | | |
|---|----|------------------------|--|--------------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (Initial Dioxin) | | |
| Initial Dioxin | n | Adj. Mean ^a | R ² | Adj. Slope (Std. Error) ^b | p-Value |
| Low | 52 | 885.8 | 0.152 | 0.041 (0.026) | 0.119 |
| Medium | 60 | 961.1 | | | |
| High | 62 | 967.0 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD4+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|-----|-------------------|-------------------------|---|----------------------|
| Dioxin Category | n | Mean ^a | Adj. Mean ^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^c | p-Value ^d |
| Comparison | 440 | 855.4 | 854.9 | | |
| Background RH | 142 | 823.0 | 830.4 | –24.5 -- | 0.421 |
| Low RH | 84 | 838.7 | 835.6 | –19.3 -- | 0.605 |
| High RH | 91 | 868.7 | 862.2 | 7.3 -- | 0.842 |
| Low plus High RH | 175 | 854.2 | 849.3 | –5.6 -- | 0.844 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | | |
|---|-----|------------------------|---|----------------------|--|
| Dioxin Category | n | Adj. Mean ^a | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^b | p-Value ^c | |
| Comparison | 436 | 897.9 | | | |
| Background RH | 140 | 854.8 | –43.1 -- | 0.176 | |
| Low RH | 83 | 893.6 | –4.3 -- | 0.911 | |
| High RH | 91 | 886.1 | –11.8 -- | 0.752 | |
| Low plus High RH | 174 | 889.7 | –8.2 -- | 0.774 | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 17-5. Analysis of CD4+ Cells (Helper T Cells) (cells/mm³) (Continued)

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | | |
|--|-----|-------------------|--|---------------------------------|---------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (1987 Dioxin +1) | | |
| 1987 Dioxin | n | Mean ^a | R ² | Slope (Std. Error) ^b | p-Value |
| Low | 110 | 813.6 | 0.004 | 0.017 (0.015) | 0.255 |
| Medium | 100 | 825.4 | | | |
| High | 107 | 882.5 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD4+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|-----|------------------------|---|--|---------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean ^a | R ² | Adjusted Slope (Std. Error) ^b | p-Value |
| Low | 108 | 821.6 | 0.091 | 0.038 (0.018) | 0.033 |
| Medium | 100 | 865.5 | | | |
| High | 106 | 944.0 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD4+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

17.2.2.1.3 CD8+ Cells (Suppressor T Cells)

All results from the analyses of CD8+ cells in Models 1 through 4 were nonsignificant (Table 17-6(a–h): p>0.11 for all analyses).

Table 17-6. Analysis of CD8+ Cells (Suppressor T Cells) (cells/mm³)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|------------|-------------------|---|----------------------|
| Occupational Category | Group | n | Mean ^a | Difference of Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>319</i> | <i>564.5</i> | <i>–22.6 --</i> | <i>0.254</i> |
| | <i>Comparison</i> | <i>455</i> | <i>587.1</i> | | |
| Officer | Ranch Hand | 135 | 558.7 | 7.0 -- | 0.818 |
| | Comparison | 164 | 551.7 | | |
| Enlisted Flyer | Ranch Hand | 56 | 563.9 | –61.7 -- | 0.207 |
| | Comparison | 78 | 625.6 | | |
| Enlisted Groundcrew | Ranch Hand | 128 | 571.0 | –30.7 -- | 0.319 |
| | Comparison | 213 | 601.7 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Table 17-6. Analysis of CD8+ Cells (Suppressor T Cells) (cells/mm³) (Continued)

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|------------|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>316</i> | <i>565.6</i> | <i>-27.4 --</i> | <i>0.169</i> |
| | <i>Comparison</i> | <i>451</i> | <i>593.0</i> | | |
| Officer | Ranch Hand | 134 | 565.9 | 7.3 -- | 0.812 |
| | Comparison | 162 | 558.6 | | |
| Enlisted Flyer | Ranch Hand | 56 | 551.8 | -72.5 -- | 0.132 |
| | Comparison | 77 | 624.3 | | |
| Enlisted Groundcrew | Ranch Hand | 126 | 564.7 | -42.2 -- | 0.170 |
| | Comparison | 212 | 606.9 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | Analysis Results for Log₂ (Initial Dioxin)^b | | |
|---|----------|-------------------------|-------------------------------|--|---------------------------------------|----------------|
| Initial Dioxin Category Summary Statistics | | | | R² | Slope (Std. Error)^c | p-Value |
| Initial Dioxin | n | Mean^a | Adj. Mean^{ab} | | | |
| Low | 52 | 531.7 | 531.9 | 0.001 | 0.012 (0.029) | 0.688 |
| Medium | 61 | 584.9 | 584.7 | | | |
| High | 62 | 568.7 | 568.7 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of CD8+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | Analysis Results for Log₂ (Initial Dioxin) | | |
|---|----------|------------------------------|--|--|--|----------------|
| Initial Dioxin Category Summary Statistics | | | | R² | Adj. Slope (Std. Error)^b | p-Value |
| Initial Dioxin | n | Adj. Mean^a | | | | |
| Low | 52 | 546.2 | | 0.039 | 0.023 (0.034) | 0.505 |
| Medium | 60 | 608.0 | | | | |
| High | 62 | 609.7 | | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD8+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-6. Analysis of CD8+ Cells (Suppressor T Cells) (cells/mm³) (Continued)

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|----------|-------------------------|-------------------------------|---|----------------------------|
| Dioxin Category | n | Mean^a | Adj. Mean^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.)^c | p-Value^d |
| Comparison | 440 | 584.2 | 584.1 | | |
| Background RH | 142 | 563.2 | 565.3 | -18.8 -- | 0.479 |
| Low RH | 84 | 572.7 | 571.8 | -12.3 -- | 0.706 |
| High RH | 91 | 554.1 | 552.4 | -31.7 -- | 0.307 |
| Low plus High RH | 175 | 562.9 | 561.6 | -22.5 -- | 0.355 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | | |
|---|----------|------------------------------|---|----------------------------|--|
| Dioxin Category | n | Adj. Mean^a | Difference of Adj. Mean vs. Comparisons (95% C.I.)^b | p-Value^c | |
| Comparison | 436 | 592.0 | | | |
| Background RH | 140 | 576.2 | -15.8 -- | 0.574 | |
| Low RH | 83 | 576.2 | -15.8 -- | 0.634 | |
| High RH | 91 | 541.9 | -50.1 -- | 0.112 | |
| Low plus High RH | 174 | 558.0 | -34.0 -- | 0.164 | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 17-6. Analysis of CD8+ Cells (Suppressor T Cells) (cells/mm³) (Continued)

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | | |
|--|----------|-------------------------|---|---------------------------------------|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Mean^a | R² | Slope (Std. Error)^b | p-Value |
| Low | 110 | 550.0 | 0.001 | 0.009 (0.019) | 0.640 |
| Medium | 100 | 571.5 | | | |
| High | 107 | 569.0 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD8+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|----------|------------------------------|---|--|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean^a | R² | Adjusted Slope (Std. Error)^b | p-Value |
| Low | 108 | 519.5 | 0.049 | 0.014 (0.022) | 0.540 |
| Medium | 100 | 553.2 | | | |
| High | 106 | 539.0 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD8+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

17.2.2.1.4 CD16+56+ Cells (Natural Killer Cells)

The Model 1 unadjusted analysis of CD16+56+ cell count revealed a marginally significant difference between Ranch Hands and Comparisons when examined across all occupational strata (Table 17-7(a): p=0.082, difference of means=-16.6 cells/mm³). In addition, a significant difference among Ranch Hands and Comparisons was found within the enlisted flyer stratum for both the unadjusted and adjusted analyses (Table 17-7(a,b): p=0.018, difference of means=-53.5 cells/mm³; p=0.011, difference of adjusted means=-58.7 cells/mm³). Each analysis displayed a higher CD16+56+ cell count mean for Comparisons. All other Model 1 contrasts and both the unadjusted and adjusted analyses from Model 2 were nonsignificant (Table 17-7(a-d): p>0.10 for all analyses).

Table 17-7. Analysis of CD16+56+ Cells (Natural Killer Cells) (cells/mm³)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|------------|-------------------|---|----------------------|
| Occupational Category | Group | n | Mean ^a | Difference of Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>319</i> | <i>259.3</i> | <i>-16.6 --</i> | <i>0.082</i> |
| | <i>Comparison</i> | <i>455</i> | <i>275.9</i> | | |
| Officer | Ranch Hand | 135 | 266.2 | -9.9 -- | 0.521 |
| | Comparison | 164 | 276.1 | | |
| Enlisted Flyer | Ranch Hand | 56 | 236.7 | -53.5 -- | 0.018 |
| | Comparison | 78 | 290.2 | | |
| Enlisted Groundcrew | Ranch Hand | 128 | 262.4 | -8.2 -- | 0.572 |
| | Comparison | 213 | 270.6 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|------------|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>316</i> | <i>265.8</i> | <i>-15.8 --</i> | <i>0.106</i> |
| | <i>Comparison</i> | <i>451</i> | <i>281.6</i> | | |
| Officer | Ranch Hand | 134 | 261.0 | -10.7 -- | 0.478 |
| | Comparison | 162 | 271.7 | | |
| Enlisted Flyer | Ranch Hand | 56 | 241.8 | -58.7 -- | 0.011 |
| | Comparison | 77 | 300.4 | | |
| Enlisted Groundcrew | Ranch Hand | 126 | 280.8 | -2.5 -- | 0.869 |
| | Comparison | 212 | 283.3 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | Analysis Results for Log₂ (Initial Dioxin)^b | | |
|---|----------|-------------------------|-------------------------------|--|---------------------------------------|----------------|
| Initial Dioxin Category Summary Statistics | | | | R² | Slope (Std. Error)^c | p-Value |
| Initial Dioxin | n | Mean^a | Adj. Mean^{ab} | | | |
| Low | 52 | 273.6 | 276.7 | 0.038 | -0.029 (0.032) | 0.370 |
| Medium | 61 | 265.1 | 263.2 | | | |
| High | 62 | 254.8 | 254.2 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of CD16+56+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-7. Analysis of CD16+56+ Cells (Natural Killer Cells) (cells/mm³) (Continued)

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | | |
|---|----------|------------------------------|--|--|----------------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (Initial Dioxin) | | |
| Initial Dioxin | n | Adj. Mean^a | R² | Adj. Slope (Std. Error)^b | p-Value |
| Low | 52 | 265.4 | 0.112 | -0.030 (0.038) | 0.429 |
| Medium | 60 | 268.8 | | | |
| High | 62 | 246.9 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD16+56+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|----------|-------------------------|-------------------------------|---|----------------------------|
| Dioxin Category | n | Mean^a | Adj. Mean^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.)^c | p-Value^d |
| Comparison | 440 | 275.8 | 275.4 | | |
| Background RH | 142 | 254.1 | 258.9 | -16.5 -- | 0.192 |
| Low RH | 84 | 283.3 | 281.1 | 5.7 -- | 0.726 |
| High RH | 91 | 247.1 | 243.3 | -32.1 -- | 0.028 |
| Low plus High RH | 175 | 263.9 | 260.7 | -14.7 -- | 0.209 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | | |
|---|----------|------------------------------|---|----------------------------|--|
| Dioxin Category | n | Adj. Mean^a | Difference of Adj. Mean vs. Comparisons (95% C.I.)^b | p-Value^c | |
| Comparison | 436 | 282.6 | | | |
| Background RH | 140 | 268.0 | -14.6 -- | 0.285 | |
| Low RH | 83 | 286.7 | 4.1 -- | 0.805 | |
| High RH | 91 | 252.0 | -30.6 -- | 0.046 | |
| Low plus High RH | 174 | 268.0 | -14.6 -- | 0.227 | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 17-7. Analysis of CD16+56+ Cells (Natural Killer Cells) (cells/mm³) (Continued)

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | | |
|--|----------|-------------------------|--|---------------------------------------|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin +1) | | |
| 1987 Dioxin | n | Mean^a | R² | Slope (Std. Error)^b | p-Value |
| Low | 110 | 258.5 | <0.001 | 0.006 (0.021) | 0.772 |
| Medium | 100 | 263.0 | | | |
| High | 107 | 257.1 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD16+56+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|----------|------------------------------|---|--|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean^a | R² | Adjusted Slope (Std. Error)^b | p-Value |
| Low | 108 | 265.6 | 0.059 | -0.001 (0.025) | 0.960 |
| Medium | 100 | 263.8 | | | |
| High | 106 | 258.6 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD16+56+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

The results from the Model 3 analysis of CD16+56+ cell count revealed similar results in the unadjusted and adjusted analyses. Comparisons were found to have a significantly higher mean CD16+56+ cell count than Ranch Hands in the high dioxin category in both the unadjusted and adjusted analyses (Table 17-7(e,f): p=0.028, difference of adjusted means=-32.1 cells/mm³; p=0.046, difference of adjusted means=-30.6 cells/mm³, respectively). All other Model 3 contrasts, as well as each analysis for Model 4, were nonsignificant (Table 17-7(e-h): p>0.19 for all analyses).

17.2.2.1.5 CD20+ Cells (B Cells)

All results from the analysis of CD20+ cell count were nonsignificant for Models 1, 3, and 4 (Table 17-8(a,b,e-h): p>0.14 for each analysis). The Model 2 unadjusted analysis revealed a significant and positive association between initial dioxin and CD20+ cell count (Table 17-8(c): p=0.024, slope=0.081). The Model 2 results became marginally significant after adjustment for covariates (Table 17-8(d): p=0.052, adjusted slope=0.075).

Table 17-8. Analysis of CD20+ Cells (B Cells) (cells/mm³)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|-----|-------------------|---|----------------------|
| Occupational Category | Group | n | Mean ^a | Difference of Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | 318 | 184.0 | -1.5 -- | 0.858 |
| | <i>Comparison</i> | 455 | 185.5 | | |
| Officer | Ranch Hand | 134 | 175.3 | 8.1 -- | 0.496 |
| | Comparison | 164 | 167.1 | | |
| Enlisted Flyer | Ranch Hand | 56 | 170.2 | -15.0 -- | 0.420 |
| | Comparison | 78 | 185.2 | | |
| Enlisted Groundcrew | Ranch Hand | 128 | 200.4 | -0.7 -- | 0.961 |
| | Comparison | 213 | 201.1 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|-----|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | 315 | 196.2 | -2.0 -- | 0.808 |
| | <i>Comparison</i> | 451 | 198.2 | | |
| Officer | Ranch Hand | 133 | 211.3 | 13.1 -- | 0.343 |
| | Comparison | 162 | 198.2 | | |
| Enlisted Flyer | Ranch Hand | 56 | 185.0 | -14.7 -- | 0.450 |
| | Comparison | 77 | 199.7 | | |
| Enlisted Groundcrew | Ranch Hand | 126 | 189.2 | -10.1 -- | 0.422 |
| | Comparison | 212 | 199.3 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | Analysis Results for Log₂ (Initial Dioxin)^b | | |
|---|----------|-------------------------|-------------------------------|--|---------------------------------------|----------------|
| Initial Dioxin Category Summary Statistics | | | | R² | Slope (Std. Error)^c | p-Value |
| Initial Dioxin | n | Mean^a | Adj. Mean^{ab} | | | |
| Low | 51 | 153.6 | 154.9 | 0.052 | 0.081 (0.035) | 0.024 |
| Medium | 61 | 198.4 | 197.3 | | | |
| High | 62 | 191.7 | 191.4 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of CD20+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-8. Analysis of CD20+ Cells (B Cells) (cells/mm³) (Continued)

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | | |
|---|----|------------------------|--|--------------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (Initial Dioxin) | | |
| Initial Dioxin | n | Adj. Mean ^a | R ² | Adj. Slope (Std. Error) ^b | p-Value |
| Low | 51 | 203.2 | 0.236 | 0.075 (0.038) | 0.052 |
| Medium | 60 | 247.8 | | | |
| High | 62 | 238.9 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD20+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|-----|-------------------|-------------------------|---|----------------------|
| Dioxin Category | n | Mean ^a | Adj. Mean ^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^c | p-Value ^d |
| Comparison | 440 | 185.0 | 185.0 | | |
| Background RH | 142 | 182.9 | 183.9 | -1.1 -- | 0.918 |
| Low RH | 83 | 167.1 | 166.7 | -18.3 -- | 0.141 |
| High RH | 91 | 196.4 | 195.5 | 10.5 -- | 0.419 |
| Low plus High RH | 174 | 181.8 | 181.1 | -3.9 -- | 0.694 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | | |
|---|-----|------------------------|---|----------------------|--|
| Dioxin Category | n | Adj. Mean ^a | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^b | p-Value ^c | |
| Comparison | 436 | 198.1 | | | |
| Background RH | 140 | 200.6 | 2.5 -- | 0.827 | |
| Low RH | 82 | 185.2 | -12.9 -- | 0.325 | |
| High RH | 91 | 194.6 | -3.5 -- | 0.788 | |
| Low plus High RH | 173 | 190.1 | -8.0 -- | 0.419 | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 17-8. Analysis of CD20+ Cells (B Cells) (cells/mm³) (Continued)

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | | |
|--|----------|-------------------------|--|---------------------------------------|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin +1) | | |
| 1987 Dioxin | n | Mean^a | R² | Slope (Std. Error)^b | p-Value |
| Low | 110 | 179.1 | 0.004 | 0.026 (0.023) | 0.260 |
| Medium | 99 | 170.0 | | | |
| High | 107 | 197.9 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD20+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|----------|------------------------------|---|--|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean^a | R² | Adjusted Slope (Std. Error)^b | p-Value |
| Low | 108 | 199.9 | 0.105 | 0.030 (0.026) | 0.253 |
| Medium | 99 | 194.4 | | | |
| High | 106 | 214.6 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD20+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

17.2.2.1.6 CD3+CD4+ Cells (Helper T Cells)

All contrasts examined within the CD3+CD4+ cell count analysis of Models 1 and 3 were nonsignificant (Table 17-9(a,b and e,f): p>0.15 for all contrasts). The Model 2 unadjusted analysis of CD3+CD4+ cell count was also nonsignificant (Table 17-9(c): p=0.226), although the adjusted analysis revealed a marginally significant and positive association between initial dioxin and the CD3+CD4+ cell count (Table 17-9(d): p=0.098, adjusted slope=0.046). The Model 4 analysis of CD3+CD4+ cell count was also nonsignificant in the unadjusted analysis (Table 17-9(g): p=0.228) and significant in the adjusted analysis, with a positive association between the 1987 dioxin levels and the CD3+CD4+ cell count (Table 17-9(h): p=0.025, adjusted slope=0.042).

Table 17-9. Analysis of CD3+CD4+ Cells (Helper T Cells) (cells/mm³)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|------------|-------------------|---|----------------------|
| Occupational Category | Group | n | Mean ^a | Difference of Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>319</i> | <i>767.4</i> | <i>-13.4 --</i> | <i>0.541</i> |
| | <i>Comparison</i> | <i>455</i> | <i>780.9</i> | | |
| Officer | Ranch Hand | 135 | 763.1 | 13.5 -- | 0.693 |
| | Comparison | 164 | 749.6 | | |
| Enlisted Flyer | Ranch Hand | 56 | 737.4 | -54.5 -- | 0.296 |
| | Comparison | 78 | 791.9 | | |
| Enlisted Groundcrew | Ranch Hand | 128 | 785.6 | -16.1 -- | 0.641 |
| | Comparison | 213 | 801.8 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|------------|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>316</i> | <i>786.5</i> | <i>-20.7 --</i> | <i>0.347</i> |
| | <i>Comparison</i> | <i>451</i> | <i>807.2</i> | | |
| Officer | Ranch Hand | 134 | 839.6 | 19.6 -- | 0.589 |
| | Comparison | 162 | 820.0 | | |
| Enlisted Flyer | Ranch Hand | 56 | 753.7 | -53.8 -- | 0.296 |
| | Comparison | 77 | 807.5 | | |
| Enlisted Groundcrew | Ranch Hand | 126 | 758.1 | -42.5 -- | 0.196 |
| | Comparison | 212 | 800.7 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | Analysis Results for Log₂ (Initial Dioxin)^b | | |
|---|----------|-------------------------|-------------------------------|--|---------------------------------------|----------------|
| Initial Dioxin Category Summary Statistics | | | | R² | Slope (Std. Error)^c | p-Value |
| Initial Dioxin | n | Mean^a | Adj. Mean^{ab} | | | |
| Low | 52 | 730.7 | 733.6 | 0.018 | 0.030 (0.024) | 0.226 |
| Medium | 61 | 807.5 | 805.4 | | | |
| High | 62 | 798.1 | 797.5 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of CD3+CD4+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-9. Analysis of CD3+CD4+ Cells (Helper T Cells) (cells/mm³) (Continued)

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | | |
|---|----|------------------------|--|--------------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (Initial Dioxin) | | |
| Initial Dioxin | n | Adj. Mean ^a | R ² | Adj. Slope (Std. Error) ^b | p-Value |
| Low | 52 | 790.9 | 0.159 | 0.046 (0.028) | 0.098 |
| Medium | 60 | 861.0 | | | |
| High | 62 | 874.2 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD3+CD4+ cells versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|-----|-------------------|-------------------------|---|----------------------|
| Dioxin Category | n | Mean ^a | Adj. Mean ^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^c | p-Value ^d |
| Comparison | 440 | 779.1 | 778.6 | | |
| Background RH | 142 | 747.7 | 753.7 | –24.9 -- | 0.395 |
| Low RH | 84 | 764.0 | 761.5 | –17.1 -- | 0.632 |
| High RH | 91 | 796.2 | 790.8 | 12.2 -- | 0.731 |
| Low plus High RH | 175 | 780.6 | 776.6 | –2.0 -- | 0.940 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | | |
|---|-----|------------------------|---|----------------------|--|
| Dioxin Category | n | Adj. Mean ^a | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^b | p-Value ^c | |
| Comparison | 436 | 809.9 | | | |
| Background RH | 140 | 766.6 | –43.3 -- | 0.151 | |
| Low RH | 83 | 806.9 | –3.0 -- | 0.935 | |
| High RH | 91 | 803.8 | –6.1 -- | 0.865 | |
| Low plus High RH | 174 | 805.3 | –4.6 -- | 0.866 | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 17-9. Analysis of CD3+CD4+ Cells (Helper T Cells) (cells/mm³) (Continued)

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | | |
|--|-----|-------------------|--|---------------------------------|---------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (1987 Dioxin +1) | | |
| 1987 Dioxin | n | Mean ^a | R ² | Slope (Std. Error) ^b | p-Value |
| Low | 110 | 738.7 | 0.005 | 0.019 (0.016) | 0.228 |
| Medium | 100 | 750.2 | | | |
| High | 107 | 809.7 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD3+CD4+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|-----|------------------------|---|--|---------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean ^a | R ² | Adjusted Slope (Std. Error) ^b | p-Value |
| Low | 108 | 731.1 | 0.097 | 0.042 (0.019) | 0.025 |
| Medium | 100 | 775.5 | | | |
| High | 106 | 854.8 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of CD3+CD4+ cells versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

17.2.2.1.7 Absolute Lymphocytes

All analysis results from Models 1 through 4 for absolute lymphocytes were nonsignificant (Table 17-10(a–h): p>0.10).

Table 17-10. Analysis of Absolute Lymphocytes (cells/mm³)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|--------------|-------------------|---|----------------------|
| Occupational Category | Group | n | Mean ^a | Difference of Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>830</i> | <i>1,781.2</i> | 3.2 -- | <i>0.909</i> |
| | <i>Comparison</i> | <i>1,199</i> | <i>1,777.9</i> | | |
| Officer | Ranch Hand | 327 | 1,730.0 | 44.8 -- | 0.292 |
| | Comparison | 475 | 1,685.2 | | |
| Enlisted Flyer | Ranch Hand | 142 | 1,753.3 | –63.8 -- | 0.360 |
| | Comparison | 178 | 1,817.2 | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 1,840.2 | –9.5 -- | 0.828 |
| | Comparison | 546 | 1,849.6 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Table 17-10. Analysis of Absolute Lymphocytes (cells/mm³) (Continued)

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|-------|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | 820 | 1,787.3 | -6.1 -- | 0.827 |
| | <i>Comparison</i> | 1,188 | 1,793.3 | | |
| Officer | Ranch Hand | 324 | 1,805.1 | 52.9 -- | 0.227 |
| | Comparison | 470 | 1,752.2 | | |
| Enlisted Flyer | Ranch Hand | 140 | 1,740.1 | -74.3 -- | 0.279 |
| | Comparison | 176 | 1,814.4 | | |
| Enlisted Groundcrew | Ranch Hand | 356 | 1,795.4 | -34.6 -- | 0.412 |
| | Comparison | 542 | 1,830.0 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | | | |
|---|-----|-------------------|-------------------------|---|---------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | | Analysis Results for Log ₂ (Initial Dioxin) ^b | | |
| Initial Dioxin | n | Mean ^a | Adj. Mean ^{ab} | R ² | Slope (Std. Error) ^c | p-Value |
| Low | 148 | 1,731.1 | 1,737.8 | 0.019 | 0.019 (0.012) | 0.121 |
| Medium | 152 | 1,777.4 | 1,777.7 | | | |
| High | 153 | 1,838.8 | 1,831.7 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of absolute lymphocytes versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | | | |
|---|-----|------------------------|--|--|--------------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | | Analysis Results for Log ₂ (Initial Dioxin) | | |
| Initial Dioxin | n | Adj. Mean ^a | | R ² | Adj. Slope (Std. Error) ^b | p-Value |
| Low | 148 | 1,742.9 | | 0.066 | 0.023 (0.014) | 0.109 |
| Medium | 150 | 1,781.8 | | | | |
| High | 151 | 1,837.5 | | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of absolute lymphocytes versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-10. Analysis of Absolute Lymphocytes (cells/mm³) (Continued)

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|-------|-------------------|-------------------------|---|----------------------|
| Dioxin Category | n | Mean ^a | Adj. Mean ^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^c | p-Value ^d |
| Comparison | 1,164 | 1,776.6 | 1,775.7 | | |
| Background RH | 371 | 1,772.5 | 1,786.3 | 10.6 -- | 0.777 |
| Low RH | 222 | 1,757.0 | 1,752.0 | -23.7 -- | 0.598 |
| High RH | 231 | 1,807.3 | 1,794.5 | 18.8 -- | 0.676 |
| Low plus High RH | 453 | 1,782.5 | 1,773.5 | -2.2 -- | 0.959 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | |
|---|-------|------------------------|---|----------------------|
| Dioxin Category | n | Adj. Mean ^a | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^b | p-Value ^c |
| Comparison | 1,154 | 1,794.7 | | |
| Background RH | 365 | 1,821.6 | 26.9 -- | 0.477 |
| Low RH | 220 | 1,768.7 | -26.0 -- | 0.562 |
| High RH | 229 | 1,755.8 | -38.9 -- | 0.389 |
| Low plus High RH | 449 | 1,762.1 | -32.6 -- | 0.340 |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | Analysis Results for Log₂ (1987 Dioxin +1) | | |
|--|----------|-------------------------|--|---------------------------------------|----------------|
| 1987 Dioxin Category Summary Statistics | | | R² | Slope (Std. Error)^b | p-Value |
| 1987 Dioxin | n | Mean^a | | | |
| Low | 281 | 1,730.6 | 0.002 | 0.010 (0.008) | 0.222 |
| Medium | 271 | 1,788.5 | | | |
| High | 272 | 1,817.6 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of absolute lymphocytes versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

Table 17-10. Analysis of Absolute Lymphocytes (cells/mm³) (Continued)

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|-----|------------------------|---|--|---------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean ^a | R ² | Adjusted Slope (Std. Error) ^b | p-Value |
| Low | 277 | 1,723.8 | 0.046 | 0.008 (0.009) | 0.393 |
| Medium | 269 | 1,783.7 | | | |
| High | 268 | 1,776.6 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of absolute lymphocytes versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

17.2.2.1.8 IgA

Examination of contrasts for Models 1 and 3 in both the unadjusted and adjusted analyses revealed no significant differences in IgA levels between Ranch Hands and Comparisons (Table 17-11(a,b and e,f): p>0.29 for all contrasts). The Model 2 unadjusted analysis of IgA was also nonsignificant (Table 17-11(c): p=0.224), although after adjustment for covariates, the association between initial dioxin and IgA levels was significant and positive (Table 17-11(d): p=0.046, adjusted slope=0.040). The Model 4 unadjusted analysis of IgA revealed a marginally significant and positive association between the 1987 dioxin levels and IgA levels (Table 17-11(g): p=0.051, adjusted slope=0.022), whereas the adjusted Model 4 analysis was nonsignificant (Table 17-11(h): p=0.115).

Table 17-11. Analysis of IgA (mg/dl)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|--------------|-------------------|---|----------------------|
| Occupational Category | Group | n | Mean ^a | Difference of Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>830</i> | <i>232.4</i> | <i>-0.9 --</i> | <i>0.860</i> |
| | <i>Comparison</i> | <i>1,199</i> | <i>233.3</i> | | |
| Officer | Ranch Hand | 327 | 224.8 | -0.4 -- | 0.958 |
| | Comparison | 475 | 225.2 | | |
| Enlisted Flyer | Ranch Hand | 142 | 238.1 | 1.4 -- | 0.912 |
| | Comparison | 178 | 236.6 | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 237.3 | -2.2 -- | 0.779 |
| | Comparison | 546 | 239.5 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Table 17-11. Analysis of IgA (mg/dl) (Continued)

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|-------|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | 820 | 234.9 | -1.4 -- | 0.790 |
| | <i>Comparison</i> | 1,188 | 236.2 | | |
| Officer | Ranch Hand | 324 | 221.5 | -2.5 -- | 0.740 |
| | Comparison | 470 | 224.0 | | |
| Enlisted Flyer | Ranch Hand | 140 | 238.2 | 0.1 -- | 0.995 |
| | Comparison | 176 | 238.1 | | |
| Enlisted Groundcrew | Ranch Hand | 356 | 246.1 | -0.7 -- | 0.927 |
| | Comparison | 542 | 246.8 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | | | |
|---|-----|-------------------|-------------------------|---|---------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | | Analysis Results for Log ₂ (Initial Dioxin) ^b | | |
| Initial Dioxin | n | Mean ^a | Adj. Mean ^{ab} | R ² | Slope (Std. Error) ^c | p-Value |
| Low | 148 | 230.8 | 231.4 | 0.007 | 0.021 (0.017) | 0.224 |
| Medium | 152 | 241.6 | 241.6 | | | |
| High | 153 | 241.1 | 240.4 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of IgA versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | | | |
|---|-----|------------------------|--|--------------------------------------|---------|--|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (Initial Dioxin) | | | |
| Initial Dioxin | n | Adj. Mean ^a | R ² | Adj. Slope (Std. Error) ^b | p-Value | |
| Low | 148 | 257.2 | 0.049 | 0.040 (0.020) | 0.046 | |
| Medium | 150 | 270.3 | | | | |
| High | 151 | 275.8 | | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of IgA versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-11. Analysis of IgA (mg/dl) (Continued)

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|-------|-------------------|-------------------------|---|----------------------|
| Dioxin Category | n | Mean ^a | Adj. Mean ^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^c | p-Value ^d |
| Comparison | 1,164 | 233.8 | 233.6 | | |
| Background RH | 371 | 225.0 | 226.8 | -6.8 -- | 0.297 |
| Low RH | 222 | 233.0 | 232.3 | -1.3 -- | 0.868 |
| High RH | 231 | 242.6 | 240.9 | 7.3 -- | 0.373 |
| Low plus High RH | 453 | 237.8 | 236.6 | 3.0 -- | 0.629 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | |
|---|-------|------------------------|---|----------------------|
| Dioxin Category | n | Adj. Mean ^a | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^b | p-Value ^c |
| Comparison | 1,154 | 236.3 | | |
| Background RH | 365 | 231.0 | -5.3 -- | 0.435 |
| Low RH | 220 | 233.2 | -3.1 -- | 0.707 |
| High RH | 229 | 241.0 | 4.7 -- | 0.575 |
| Low plus High RH | 449 | 237.1 | 0.8 -- | 0.890 |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | | |
|--|-----|-------------------|--|---------------------------------|---------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (1987 Dioxin +1) | | |
| 1987 Dioxin | n | Mean ^a | R ² | Slope (Std. Error) ^b | p-Value |
| Low | 281 | 221.1 | 0.005 | 0.022 (0.011) | 0.051 |
| Medium | 271 | 231.1 | | | |
| High | 272 | 244.7 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of IgA versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

Table 17-11. Analysis of IgA (mg/dl) (Continued)

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|----------|------------------------------|---|--|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean^a | R² | Adjusted Slope (Std. Error)^b | p-Value |
| Low | 277 | 240.7 | 0.031 | 0.021 (0.013) | 0.115 |
| Medium | 269 | 247.3 | | | |
| High | 268 | 265.1 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of IgA versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

17.2.2.1.9 IgG

All analyses of IgG from Models 1 through 4 were nonsignificant (Table 17-12 (a–h): p>0.21).

Table 17-12. Analysis of IgG (mg/dl)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|--------------|-------------------------|---|----------------------------|
| Occupational Category | Group | n | Mean^a | Difference of Means (95% C.I.)^b | p-Value^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>830</i> | <i>1,035.5</i> | <i>-11.8 --</i> | <i>0.273</i> |
| | <i>Comparison</i> | <i>1,199</i> | <i>1,047.3</i> | | |
| Officer | Ranch Hand | 327 | 1,022.2 | -7.7 -- | 0.649 |
| | Comparison | 475 | 1,029.8 | | |
| Enlisted Flyer | Ranch Hand | 142 | 1,021.8 | -27.2 -- | 0.307 |
| | Comparison | 178 | 1,048.9 | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 1,053.3 | -8.9 -- | 0.587 |
| | Comparison | 546 | 1,062.2 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Table 17-12. Analysis of IgG (mg/dl) (Continued)

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|-------|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | 820 | 1,121.4 | -13.9 -- | 0.217 |
| | <i>Comparison</i> | 1,188 | 1,135.4 | | |
| Officer | Ranch Hand | 324 | 1,101.3 | -14.3 -- | 0.417 |
| | Comparison | 470 | 1,115.6 | | |
| Enlisted Flyer | Ranch Hand | 140 | 1,111.7 | -32.3 -- | 0.251 |
| | Comparison | 176 | 1,144.1 | | |
| Enlisted Groundcrew | Ranch Hand | 356 | 1,145.3 | -6.8 -- | 0.694 |
| | Comparison | 542 | 1,152.2 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | | | |
|---|-----|-------------------|-------------------------|---|---------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | | Analysis Results for Log ₂ (Initial Dioxin) ^b | | |
| Initial Dioxin | n | Mean ^a | Adj. Mean ^{ab} | R ² | Slope (Std. Error) ^c | p-Value |
| Low | 148 | 1,040.7 | 1,039.6 | 0.002 | -0.001 (0.009) | 0.922 |
| Medium | 152 | 1,061.9 | 1,061.8 | | | |
| High | 153 | 1,025.2 | 1,026.3 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of IgG versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | | | |
|---|-----|------------------------|--|--|--------------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | | Analysis Results for Log ₂ (Initial Dioxin) | | |
| Initial Dioxin | n | Adj. Mean ^a | | R ² | Adj. Slope (Std. Error) ^b | p-Value |
| Low | 148 | 1,132.3 | | 0.119 | -0.003 (0.010) | 0.761 |
| Medium | 150 | 1,162.9 | | | | |
| High | 151 | 1,107.0 | | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of IgG versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-12. Analysis of IgG (mg/dl) (Continued)

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|-------|-------------------|-------------------------|---|----------------------|
| Dioxin Category | n | Mean ^a | Adj. Mean ^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^c | p-Value ^d |
| Comparison | 1,164 | 1,048.3 | 1,048.1 | | |
| Background RH | 371 | 1,029.2 | 1,031.9 | -16.2 -- | 0.254 |
| Low RH | 222 | 1,042.7 | 1,041.7 | -6.4 -- | 0.713 |
| High RH | 231 | 1,042.2 | 1,039.6 | -8.5 -- | 0.621 |
| Low plus High RH | 453 | 1,042.5 | 1,040.7 | -7.4 -- | 0.572 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | | |
|---|-------|------------------------|---|----------------------|--|
| Dioxin Category | n | Adj. Mean ^a | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^b | p-Value ^c | |
| Comparison | 1,154 | 1,136.6 | | | |
| Background RH | 365 | 1,122.1 | -14.5 -- | 0.340 | |
| Low RH | 220 | 1,121.4 | -15.2 -- | 0.404 | |
| High RH | 229 | 1,125.1 | -11.5 -- | 0.535 | |
| Low plus High RH | 449 | 1,123.3 | -13.3 -- | 0.340 | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | Analysis Results for Log₂ (1987 Dioxin +1) | | |
|--|----------|-------------------------|--|---------------------------------------|----------------|
| 1987 Dioxin Category Summary Statistics | | | R² | Slope (Std. Error)^b | p-Value |
| 1987 Dioxin | n | Mean^a | | | |
| Low | 281 | 1,019.6 | <0.001 | 0.002 (0.005) | 0.652 |
| Medium | 271 | 1,040.5 | | | |
| High | 272 | 1,050.1 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of IgG versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

Table 17-12. Analysis of IgG (mg/dl) (Continued)

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|----------|------------------------------|---|--|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean^a | R² | Adjusted Slope (Std. Error)^b | p-Value |
| Low | 277 | 1,115.5 | 0.073 | -0.001 (0.006) | 0.920 |
| Medium | 269 | 1,132.4 | | | |
| High | 268 | 1,142.7 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of IgG versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

17.2.2.1.10 IgM

Each result from the analyses of IgM was nonsignificant for Models 1 through 4 (Table 17-13 (a–h): p>0.10 for all analyses).

Table 17-13. Analysis of IgM (mg/dl)

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|--------------|-------------------------|---|----------------------------|
| Occupational Category | Group | n | Mean^a | Difference of Means (95% C.I.)^b | p-Value^c |
| <i>All</i> | <i>Ranch Hand</i> | <i>830</i> | <i>96.3</i> | <i>-2.1 --</i> | <i>0.373</i> |
| | <i>Comparison</i> | <i>1,199</i> | <i>98.4</i> | | |
| Officer | Ranch Hand | 327 | 95.2 | -0.6 -- | 0.862 |
| | Comparison | 475 | 95.9 | | |
| Enlisted Flyer | Ranch Hand | 142 | 94.6 | -9.7 -- | 0.102 |
| | Comparison | 178 | 104.4 | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 98.0 | -0.8 -- | 0.831 |
| | Comparison | 546 | 98.7 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Table 17-13. Analysis of IgM (mg/dl) (Continued)

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | | | |
|--|-------------------|-------|----------------------------|--|----------------------|
| Occupational Category | Group | n | Adjusted Mean ^a | Difference of Adj. Means (95% C.I.) ^b | p-Value ^c |
| <i>All</i> | <i>Ranch Hand</i> | 820 | 90.5 | -2.0 -- | 0.365 |
| | <i>Comparison</i> | 1,188 | 92.4 | | |
| Officer | Ranch Hand | 324 | 89.2 | -0.7 -- | 0.831 |
| | Comparison | 470 | 89.9 | | |
| Enlisted Flyer | Ranch Hand | 140 | 89.3 | -8.7 -- | 0.120 |
| | Comparison | 176 | 98.1 | | |
| Enlisted Groundcrew | Ranch Hand | 356 | 90.7 | -0.7 -- | 0.824 |
| | Comparison | 542 | 91.4 | | |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | | | |
|---|-----|-------------------|-------------------------|---|---------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | | Analysis Results for Log ₂ (Initial Dioxin) ^b | | |
| Initial Dioxin | n | Mean ^a | Adj. Mean ^{ab} | R ² | Slope (Std. Error) ^c | p-Value |
| Low | 148 | 93.9 | 93.5 | 0.005 | 0.007 (0.019) | 0.711 |
| Medium | 152 | 96.5 | 96.5 | | | |
| High | 153 | 96.0 | 96.3 | | | |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Slope and standard error based on natural logarithm of IgM versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | | | | | |
|---|-----|------------------------|--|--|--------------------------------------|---------|
| Initial Dioxin Category Summary Statistics | | | | Analysis Results for Log ₂ (Initial Dioxin) | | |
| Initial Dioxin | n | Adj. Mean ^a | | R ² | Adj. Slope (Std. Error) ^b | p-Value |
| Low | 148 | 86.3 | | 0.046 | -0.003 (0.022) | 0.896 |
| Medium | 150 | 89.7 | | | | |
| High | 151 | 87.9 | | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of IgM versus log₂ (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 17-13. Analysis of IgM (mg/dl) (Continued)

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | | |
|---|-------|-------------------|-------------------------|---|----------------------|
| Dioxin Category | n | Mean ^a | Adj. Mean ^{ab} | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^c | p-Value ^d |
| Comparison | 1,164 | 98.2 | 98.2 | | |
| Background RH | 371 | 97.1 | 96.1 | -2.1 -- | 0.487 |
| Low RH | 222 | 95.5 | 95.8 | -2.4 -- | 0.525 |
| High RH | 231 | 95.5 | 96.4 | -1.8 -- | 0.619 |
| Low plus High RH | 453 | 95.5 | 96.1 | -2.1 -- | 0.459 |

^a Transformed from natural logarithm scale.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^d P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | |
|---|-------|------------------------|---|----------------------|
| Dioxin Category | n | Adj. Mean ^a | Difference of Adj. Mean vs. Comparisons (95% C.I.) ^b | p-Value ^c |
| Comparison | 1,154 | 92.5 | | |
| Background RH | 365 | 91.2 | -1.3 -- | 0.659 |
| Low RH | 220 | 90.7 | -1.8 -- | 0.599 |
| High RH | 229 | 89.4 | -3.1 -- | 0.390 |
| Low plus High RH | 449 | 90.0 | -2.5 -- | 0.358 |

^a Transformed from natural logarithm scale.

^b Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.

^c P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | Analysis Results for Log₂ (1987 Dioxin +1) | | |
|--|----------|-------------------------|--|---------------------------------------|----------------|
| 1987 Dioxin Category Summary Statistics | | | R² | Slope (Std. Error)^b | p-Value |
| 1987 Dioxin | n | Mean^a | | | |
| Low | 281 | 96.4 | <0.001 | -0.001 (0.012) | 0.937 |
| Medium | 271 | 96.4 | | | |
| High | 272 | 95.7 | | | |

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of IgM versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

Table 17-13. Analysis of IgM (mg/dl) (Continued)

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | | | |
|--|----------|------------------------------|---|--|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | | |
| 1987 Dioxin | n | Adj. Mean^a | R² | Adjusted Slope (Std. Error)^b | p-Value |
| Low | 277 | 88.6 | 0.025 | -0.008 (0.014) | 0.586 |
| Medium | 269 | 89.3 | | | |
| High | 268 | 86.4 | | | |

^a Transformed from natural logarithm scale

^b Slope and standard error based on natural logarithm of IgM versus log₂ (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

17.2.2.1.11 Lupus Panel: ANA Test

All analysis results from Models 1 through 4 for the antinuclear antibody were nonsignificant (Table 17-14(a–h): p>0.20).

Table 17-14. Analysis of Lupus Panel: ANA Test

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|--------------|---------------------------|--------------------------------------|----------------|
| Occupational Category | Group | n | Number (%) Present | Est. Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | <i>Ranch Hand</i> | <i>830</i> | <i>432 (52.1)</i> | <i>1.00 (0.84,1.19)</i> | <i>0.998</i> |
| | <i>Comparison</i> | <i>1,199</i> | <i>624 (52.0)</i> | | |
| Officer | Ranch Hand | 327 | 168 (51.4) | 0.94 (0.71,1.25) | 0.683 |
| | Comparison | 475 | 251 (52.8) | | |
| Enlisted Flyer | Ranch Hand | 142 | 73 (51.4) | 1.11 (0.71,1.72) | 0.653 |
| | Comparison | 178 | 87 (48.9) | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 191 (52.9) | 1.02 (0.78,1.33) | 0.876 |
| | Comparison | 546 | 286 (52.4) | | |

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | |
|--|--|----------------|
| Occupational Category | Adjusted Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | <i>1.01 (0.84,1.20)</i> | <i>0.946</i> |
| Officer | 0.95 (0.72,1.27) | 0.736 |
| Enlisted Flyer | 1.07 (0.68,1.67) | 0.778 |
| Enlisted Groundcrew | 1.04 (0.79,1.36) | 0.801 |

Table 17-14. Analysis of Lupus Panel: ANA Test (Continued)

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | |
|---|-----|--------------------|---|---------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (Initial Dioxin) ^a | |
| Initial Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.) ^b | p-Value |
| Low | 148 | 76 (51.4) | 1.08 (0.94,1.24) | 0.301 |
| Medium | 152 | 71 (46.7) | | |
| High | 153 | 85 (55.6) | | |

^a Adjusted for percent body fat at the time of the blood measurement of dioxin.

^b Relative risk for a twofold increase in initial dioxin.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | |
|---|--|---------|
| Analysis Results for Log ₂ (Initial Dioxin) | | |
| n | Adjusted Relative Risk (95% C.I.) ^a | p-Value |
| 449 | 1.04 (0.88,1.24) | 0.622 |

^a Relative risk for a twofold increase in initial dioxin.

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | |
|---|-------|--------------------|---|---------|
| Dioxin Category | n | Number (%) Present | Est. Relative Risk (95% C.I.) ^{ab} | p-Value |
| Comparison | 1,164 | 606 (52.1) | | |
| Background RH | 371 | 199 (53.6) | 1.05 (0.83,1.33) | 0.674 |
| Low RH | 222 | 105 (47.3) | 0.83 (0.62,1.11) | 0.202 |
| High RH | 231 | 127 (55.0) | 1.14 (0.85,1.51) | 0.380 |
| Low plus High RH | 453 | 232 (51.2) | 0.97 (0.78,1.21) | 0.810 |

^a Relative risk and confidence interval relative to Comparisons.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | |
|---|-------|--|---------|
| Dioxin Category | n | Adjusted Relative Risk (95% C.I.) ^a | p-Value |
| Comparison | 1,154 | | |
| Background RH | 365 | 1.04 (0.82,1.33) | 0.738 |
| Low RH | 220 | 0.85 (0.63,1.14) | 0.276 |
| High RH | 229 | 1.15 (0.85,1.55) | 0.364 |
| Low plus High RH | 449 | 0.99 (0.79,1.24) | 0.936 |

^a Relative risk and confidence interval relative to Comparisons.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 17-14. Analysis of Lupus Panel: ANA Test (Continued)

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | |
|--|-----|--------------------|---|---------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (1987 Dioxin + 1) | |
| 1987 Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.) ^a | p-Value |
| Low | 281 | 153 (54.5) | 0.98 (0.90,1.08) | 0.732 |
| Medium | 271 | 134 (49.5) | | |
| High | 272 | 144 (52.9) | | |

^a Relative risk for a twofold increase in 1987 dioxin.

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | |
|--|--|--|---------|
| Analysis Results for Log ₂ (1987 Dioxin + 1) | | | |
| n | Adjusted Relative Risk (95% C.I.) ^a | | p-Value |
| 814 | 0.96 (0.86,1.08) | | 0.512 |

^a Relative risk for a twofold increase in 1987 dioxin.

17.2.2.1.12 Lupus Panel: Thyroid Microsomal Antibody

All results from the analyses of the thyroid microsomal antibody from Models 1 through 4 were nonsignificant (Table 17-15(a–h): p>0.27).

Table 17-15. Analysis of Lupus Panel: ANA Thyroid Microsomal Antibody

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|-------|--------------------|-------------------------------|---------|
| Occupational Category | Group | n | Number (%) Present | Est. Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | <i>Ranch Hand</i> | 830 | 24 (2.9) | 1.02 (0.60,1.73) | 0.941 |
| | <i>Comparison</i> | 1,199 | 34 (2.8) | | |
| Officer | Ranch Hand | 327 | 11 (3.4) | 1.15 (0.51,2.56) | 0.739 |
| | Comparison | 475 | 14 (3.0) | | |
| Enlisted Flyer | Ranch Hand | 142 | 3 (2.1) | 0.75 (0.18,3.18) | 0.693 |
| | Comparison | 178 | 5 (2.8) | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 10 (2.8) | 1.01 (0.45,2.27) | 0.984 |
| | Comparison | 546 | 15 (2.8) | | |

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | |
|--|-----------------------------------|--|---------|
| Occupational Category | Adjusted Relative Risk (95% C.I.) | | p-Value |
| <i>All</i> | 1.02 (0.59,1.75) | | 0.947 |
| Officer | 1.14 (0.51,2.55) | | 0.750 |
| Enlisted Flyer | 0.75 (0.17,3.19) | | 0.692 |
| Enlisted Groundcrew | 1.00 (0.43,2.35) | | 0.994 |

Table 17-15. Analysis of Lupus Panel: ANA Thyroid Microsomal Antibody (Continued)

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | |
|---|-----|--------------------|---|---------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (Initial Dioxin) ^a | |
| Initial Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.) ^b | p-Value |
| Low | 148 | 6 (4.1) | 0.77 (0.47,1.26) | 0.272 |
| Medium | 152 | 3 (2.0) | | |
| High | 153 | 3 (2.0) | | |

^a Adjusted for percent body fat at the time of the blood measurement of dioxin.

^b Relative risk for a twofold increase in initial dioxin.

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | |
|---|--|---------|
| Analysis Results for Log ₂ (Initial Dioxin) | | |
| n | Adjusted Relative Risk (95% C.I.) ^a | p-Value |
| 449 | 0.77 (0.43,1.35) | 0.344 |

^a Relative risk for a twofold increase in initial dioxin.

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | |
|---|-------|--------------------|---|---------|
| Dioxin Category | n | Number (%) Present | Est. Relative Risk (95% C.I.) ^{ab} | p-Value |
| Comparison | 1,164 | 34 (2.9) | | |
| Background RH | 371 | 12 (3.2) | 1.13 (0.58,2.22) | 0.717 |
| Low RH | 222 | 7 (3.2) | 1.08 (0.47,2.46) | 0.862 |
| High RH | 231 | 5 (2.2) | 0.72 (0.28,1.88) | 0.506 |
| Low plus High RH | 453 | 12 (2.7) | 0.88 (0.45,1.73) | 0.709 |

^a Relative risk and confidence interval relative to Comparisons.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 17-15. Analysis of Lupus Panel: ANA Thyroid Microsomal Antibody (Continued)

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | |
|---|----------|--|----------------|
| Dioxin Category | n | Adjusted Relative Risk (95% C.I.)^a | p-Value |
| Comparison | 1,154 | | |
| Background RH | 365 | 1.03 (0.51,2.12) | 0.925 |
| Low RH | 220 | 1.12 (0.49,2.59) | 0.785 |
| High RH | 229 | 0.81 (0.30,2.16) | 0.671 |
| Low plus High RH | 449 | 0.95 (0.48,1.90) | 0.883 |

^a Relative risk and confidence interval relative to Comparisons.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | |
|--|----------|---------------------------|---|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) |
| 1987 Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.)^a |
| Low | 281 | 8 (2.9) | 0.90 (0.68,1.20) |
| Medium | 271 | 10 (3.7) | |
| High | 272 | 6 (2.2) | |

^a Relative risk for a twofold increase in 1987 dioxin.

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | |
|---|--|----------------|
| Analysis Results for Log₂ (1987 Dioxin + 1) | | |
| n | Adjusted Relative Risk (95% C.I.)^a | p-Value |
| 814 | 0.96 (0.69,1.35) | 0.824 |

^a Relative risk for a twofold increase in 1987 dioxin.

17.2.2.1.13 Lupus Panel: MSK Smooth Muscle Antibody

The Model 1 analysis revealed a significant difference in the presence of the MSK smooth muscle antibody between Ranch Hands (8.5%) and Comparisons (16.3%) in the enlisted flyer stratum. The analyses were significant both unadjusted and adjusted for covariates (Table 17-16(a,b): p=0.040, Est. RR=0.47; p=0.045, Adj. RR=0.48, respectively). All other Model 1 contrasts were nonsignificant (Table 17-16(a,b): p>0.21).

Table 17-16. Analysis of Lupus Panel: MSK Smooth Muscle Antibody

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|--------------|--------------------|-------------------------------|--------------|
| Occupational Category | Group | n | Number (%) Present | Est. Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | <i>Ranch Hand</i> | <i>830</i> | <i>101 (12.2)</i> | <i>1.01 (0.77,1.32)</i> | <i>0.959</i> |
| | <i>Comparison</i> | <i>1,199</i> | <i>145 (12.1)</i> | | |
| Officer | Ranch Hand | 327 | 43 (13.2) | 1.32 (0.85,2.04) | 0.217 |
| | Comparison | 475 | 49 (10.3) | | |
| Enlisted Flyer | Ranch Hand | 142 | 12 (8.5) | 0.47 (0.23,0.97) | 0.040 |
| | Comparison | 178 | 29 (16.3) | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 46 (12.7) | 1.04 (0.70,1.56) | 0.833 |
| | Comparison | 546 | 67 (12.3) | | |

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | |
|--|-----------------------------------|--------------|
| Occupational Category | Adjusted Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | <i>0.99 (0.75,1.31)</i> | <i>0.953</i> |
| Officer | 1.30 (0.84,2.03) | 0.239 |
| Enlisted Flyer | 0.48 (0.24,0.99) | 0.045 |
| Enlisted Groundcrew | 1.02 (0.68,1.53) | 0.934 |

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | |
|---|-----|--------------------|---|---------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (Initial Dioxin) ^a | |
| Initial Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.) ^b | p-Value |
| Low | 148 | 18 (12.2) | 0.80 (0.62,1.02) | 0.061 |
| Medium | 152 | 20 (13.2) | | |
| High | 153 | 11 (7.2) | | |

^a Adjusted for percent body fat at the time of the blood measurement of dioxin.

^b Relative risk for a twofold increase in initial dioxin.

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | |
|---|--|---------|
| Analysis Results for Log ₂ (Initial Dioxin) | | |
| n | Adjusted Relative Risk (95% C.I.) ^a | p-Value |
| 449 | 0.77 (0.58,1.04) | 0.082 |

^a Relative risk for a twofold increase in initial dioxin.

Table 17-16. Analysis of Lupus Panel: MSK Smooth Muscle Antibody (Continued)

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | |
|---|----------|---------------------------|---|----------------|
| Dioxin Category | n | Number (%) Present | Est. Relative Risk (95% C.I.)^{ab} | p-Value |
| Comparison | 1,164 | 141 (12.1) | | |
| Background RH | 371 | 52 (14.0) | 1.23 (0.87,1.74) | 0.235 |
| Low RH | 222 | 30 (13.5) | 1.12 (0.73,1.71) | 0.601 |
| High RH | 231 | 19 (8.2) | 0.63 (0.38,1.04) | 0.071 |
| Low plus High RH | 453 | 49 (10.8) | 0.83 (0.59,1.19) | 0.315 |

^a Relative risk and confidence interval relative to Comparisons.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | |
|---|----------|--|--|----------------|
| Dioxin Category | n | Adjusted Relative Risk (95% C.I.)^a | | p-Value |
| Comparison | 1,154 | | | |
| Background RH | 365 | 1.28 (0.90,1.83) | | 0.173 |
| Low RH | 220 | 1.07 (0.70,1.65) | | 0.752 |
| High RH | 229 | 0.59 (0.36,1.00) | | 0.048 |
| Low plus High RH | 449 | 0.79 (0.55,1.14) | | 0.209 |

^a Relative risk and confidence interval relative to Comparisons.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | |
|--|----------|---------------------------|---|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | |
| 1987 Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.)^a | p-Value |
| Low | 281 | 34 (12.1) | 0.88 (0.76,1.02) | 0.087 |
| Medium | 271 | 38 (14.0) | | |
| High | 272 | 29 (10.7) | | |

^a Relative risk for a twofold increase in 1987 dioxin.

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

Table 17-16. Analysis of Lupus Panel: MSK Smooth Muscle Antibody (Continued)

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | |
|--|---|---------|
| Analysis Results for Log ₂ (1987 Dioxin + 1) | | |
| n | Adjusted Relative Risk (95% C.I.) ^a | p-Value |
| 814 | 0.89 (0.75,1.05) | 0.155 |

^a Relative risk for a twofold increase in 1987 dioxin.

A marginally significant and inverse association was found between initial dioxin and the presence of the MSK smooth muscle antibody in both the unadjusted and adjusted analyses of Model 2 (Table 17-16(c,d): p=0.061, Est. RR=0.80; p=0.082, Adj. RR=0.77, respectively). As initial dioxin increased, the percentage of Ranch Hands with the MSK smooth muscle antibody present decreased.

The unadjusted analysis of Model 3 uncovered a marginally significant difference in the presence of the MSK smooth muscle antibody between Ranch Hands in the high dioxin category (8.2%) and Comparisons (12.1%) (Table 17-16(e): p=0.071, Est. RR=0.63). After adjustment for covariates, the association became significant (Table 17-16(f): p=0.048, Adj. RR=0.59). All other Model 3 contrasts were nonsignificant in both unadjusted and adjusted analyses (Table 17-16(e,f): p>0.17 for all contrasts).

The Model 4 unadjusted analysis revealed a marginally significant association between the 1987 dioxin levels and the presence of the MSK smooth muscle antibody (Table 17-16(g): p=0.087, Est. RR=0.88). After adjustment for covariates, the association was nonsignificant (Table 17-16(h): p=0.155).

17.2.2.1.14 Lupus Panel: MSK Mitochondrial Antibody

Due to the sparseness of the presence of the MSK mitochondrial antibody among the study participants, analyses were limited. The Model 1 adjusted analysis of MSK mitochondrial antibody displayed a marginally significant difference in the presence of the antibody between Ranch Hands (1.2%) and Comparisons (0.2%) in the officer stratum (Table 17-17(b): p=0.098, Adj. RR=6.58). All other Model 1 analyses performed were nonsignificant (Table 17-17(a,b): p>0.11).

Table 17-17. Analysis of Lupus Panel: MSK Mitochondrial Antibody

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|-------|--------------------|-------------------------------|--------------------|
| Occupational Category | Group | n | Number (%) Present | Est. Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | <i>Ranch Hand</i> | 830 | 4 (0.5) | 2.90 (0.53,15.86) | 0.203 |
| | <i>Comparison</i> | 1,199 | 2 (0.2) | | |
| Officer | Ranch Hand | 327 | 4 (1.2) | 5.87 (0.65,52.76) | 0.114 |
| | Comparison | 475 | 1 (0.2) | | |
| Enlisted Flyer | Ranch Hand | 142 | 0 (0.0) | -- | 0.999 ^a |
| | Comparison | 178 | 1 (0.6) | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 0 (0.0) | -- | -- |
| | Comparison | 546 | 0 (0.0) | | |

^a P-value determined using a chi-square test with continuity correction because of the sparse number of participants with the MSK mitochondrial antibody present.

--: Results not presented because of the sparse number of participants with the MSK mitochondrial antibody present.

Table 17-17. Analysis of Lupus Panel: MSK Mitochondrial Antibody (Continued)

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | |
|--|--|----------------|
| Occupational Category | Adjusted Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | 2.79 (0.51,15.31) | 0.222 |
| Officer | 6.58 (0.70,61.53) | 0.098 |
| Enlisted Flyer | -- | -- |
| Enlisted Groundcrew | -- | -- |

--: Results not presented because of the sparse number of participants with the MSK mitochondrial antibody present.

Note: Results are not adjusted for race, occupation (contrast of all Ranch Hands with all Comparisons), current alcohol use, and physical activity index because of the sparse number of participants with the MSK mitochondrial antibody present.

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | |
|---|----------|---------------------------|--|----------------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (Initial Dioxin)^a | |
| Initial Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.)^b | p-Value |
| Low | 148 | 2 (1.4) | 0.11 (0.01,4.01) | 0.034 |
| Medium | 152 | 0 (0.0) | | |
| High | 153 | 0 (0.0) | | |

^a Adjusted for percent body fat at the time of the blood measurement of dioxin.

^b Relative risk for a twofold increase in initial dioxin.

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | |
|--|--|----------------|
| Analysis Results for Log₂ (Initial Dioxin) | | |
| n | Adjusted Relative Risk (95% C.I.)^a | p-Value |
| 450 | 0.10 (0.01,4.01) | 0.049 |

^a Relative risk for a twofold increase in initial dioxin.

Note: Results are not adjusted for race, current alcohol use, and physical activity index due to the sparse number of participants with the MSK mitochondrial antibody present.

Table 17-17. Analysis of Lupus Panel: MSK Mitochondrial Antibody (Continued)

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | |
|---|----------|---------------------------|---|--------------------|
| Dioxin Category | n | Number (%) Present | Est. Relative Risk (95% C.I.)^{ab} | p-Value |
| Comparison | 1,164 | 2 (0.2) | | |
| Background RH | 371 | 2 (0.5) | 3.74 (0.51,27.25) | 0.193 |
| Low RH | 222 | 2 (0.9) | 4.91 (0.68,35.44) | 0.114 |
| High RH | 231 | 0 (0.0) | -- | 0.999 ^c |
| Low plus High RH | 453 | 2 (0.4) | -- | 0.672 ^c |

^a Relative risk and confidence interval relative to Comparisons.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

^c P-value determined using a chi-square test with continuity correction because of the sparse number of participants with the MSK mitochondrial antibody present.

--: Results not presented because of the sparse number of participants with the MSK mitochondrial antibody present.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | | |
|---|----------|--|--|----------------|
| Dioxin Category | n | Adjusted Relative Risk (95% C.I.)^a | | p-Value |
| Comparison | 1,154 | | | |
| Background RH | 365 | 3.55 (0.48,26.04) | | 0.213 |
| Low RH | 220 | 4.30 (0.57,32.27) | | 0.156 |
| High RH | 229 | -- | | -- |
| Low plus High RH | 449 | -- | | -- |

^a Relative risk and confidence interval relative to Comparisons.

--: Results not presented because of the sparse number of participants with the MSK mitochondrial antibody present.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Results are not adjusted for race, occupation, current alcohol, and physical activity index because of the sparse number of participants with the MSK mitochondrial antibody present.

Table 17-17. Analysis of Lupus Panel: MSK Mitochondrial Antibody (Continued)

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | |
|--|----------|---------------------------|---|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | |
| 1987 Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.)^a | p-Value |
| Low | 281 | 1 (0.4) | 0.62 (0.29,1.33) | 0.206 |
| Medium | 271 | 3 (1.1) | | |
| High | 272 | 0 (0.0) | | |

^a Relative risk for a twofold increase in 1987 dioxin.

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | |
|---|--|--|----------------|
| Analysis Results for Log₂ (1987 Dioxin + 1) | | | |
| n | Adjusted Relative Risk (95% C.I.)^a | | p-Value |
| 814 | 0.65 (0.31,1.37) | | 0.245 |

^a Relative risk for a twofold increase in 1987 dioxin.

Note: Results are not adjusted for race, occupation, current alcohol, and physical activity index because of the sparse number of participants with the MSK mitochondrial antibody present.

The Model 2 analysis of MSK mitochondrial antibody showed a significant inverse association with initial dioxin (Est. RR=0.11, p=0.034, unadjusted; Adj. RR=0.10, p=0.049, adjusted). The percentage of participants with MSK mitochondrial antibody increased as initial dioxin decreased.

All Model 3 and 4 analyses were nonsignificant (Table 17-17 (e,h): p>0.11).

17.2.2.1.15 Lupus Panel: MSK Parietal Antibody

The Model 1 unadjusted and adjusted analyses of the MSK parietal antibody found no significant differences between Ranch Hands and Comparisons examined across all occupations and within each occupational stratum (Table 17-18(a,b): p>0.33). Results were also nonsignificant for the Model 2 and 4 analyses of MSK parietal antibody (Table 17-18(c,d and g,h): p≥0.14).

Table 17-18. Analysis of Lupus Panel: MSK Parietal Antibody

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|-------|--------------------|-------------------------------|---------|
| Occupational Category | Group | n | Number (%) Present | Est. Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | <i>Ranch Hand</i> | 830 | 36 (4.3) | 1.02 (0.66,1.58) | 0.927 |
| | <i>Comparison</i> | 1,199 | 51 (4.3) | | |
| Officer | Ranch Hand | 327 | 14 (4.3) | 1.37 (0.65,2.88) | 0.404 |
| | Comparison | 475 | 15 (3.2) | | |
| Enlisted Flyer | Ranch Hand | 142 | 5 (3.5) | 0.61 (0.20,1.84) | 0.382 |
| | Comparison | 178 | 10 (5.6) | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 17 (4.7) | 0.99 (0.53,1.85) | 0.971 |
| | Comparison | 546 | 26 (4.8) | | |

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | | |
|--|-----------------------------------|--|---------|
| Occupational Category | Adjusted Relative Risk (95% C.I.) | | p-Value |
| <i>All</i> | 1.00 (0.64,1.56) | | 0.996 |
| Officer | 1.36 (0.65,2.87) | | 0.416 |
| Enlisted Flyer | 0.58 (0.19,1.74) | | 0.331 |
| Enlisted Groundcrew | 0.97 (0.51,1.85) | | 0.920 |

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | |
|---|-----|--------------------|---|---------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log ₂ (Initial Dioxin) ^a | |
| Initial Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.) ^b | p-Value |
| Low | 148 | 10 (6.8) | 0.86 (0.63,1.18) | 0.335 |
| Medium | 152 | 10 (6.6) | | |
| High | 153 | 6 (3.9) | | |

^a Adjusted for percent body fat at the time of the blood measurement of dioxin.

^b Relative risk for a twofold increase in initial dioxin.

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | |
|---|--|---------|
| Analysis Results for Log ₂ (Initial Dioxin) | | |
| n | Adjusted Relative Risk (95% C.I.) ^a | p-Value |
| 449 | 0.93 (0.64,1.35) | 0.694 |

^a Relative risk for a twofold increase in initial dioxin.

Table 17-18. Analysis of Lupus Panel: MSK Parietal Antibody (Continued)

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | |
|---|----------|---------------------------|---|----------------|
| Dioxin Category | n | Number (%) Present | Est. Relative Risk (95% C.I.)^{ab} | p-Value |
| Comparison | 1,164 | 50 (4.3) | | |
| Background RH | 371 | 9 (2.4) | 0.61 (0.29,1.25) | 0.179 |
| Low RH | 222 | 16 (7.2) | 1.68 (0.94,3.02) | 0.082 |
| High RH | 231 | 10 (4.3) | 0.93 (0.46,1.87) | 0.843 |
| Low plus High RH | 453 | 26 (5.7) | 1.24 (0.75,2.05) | 0.392 |

^a Relative risk and confidence interval relative to Comparisons.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | |
|---|----------|--|----------------|
| Dioxin Category | n | Adjusted Relative Risk (95% C.I.)^a | p-Value |
| Comparison | 1,154 | | |
| Background RH | 365 | 0.63 (0.30,1.31) | 0.216 |
| Low RH | 220 | 1.50 (0.82,2.75) | 0.192 |
| High RH | 229 | 0.97 (0.47,1.99) | 0.928 |
| Low plus High RH | 449 | 1.20 (0.72,2.00) | 0.490 |

^a Relative risk and confidence interval relative to Comparisons.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | |
|--|----------|---------------------------|---|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | |
| 1987 Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.)^a | p-Value |
| Low | 281 | 6 (2.1) | 1.14 (0.92,1.42) | 0.245 |
| Medium | 271 | 15 (5.5) | | |
| High | 272 | 14 (5.2) | | |

^a Relative risk for a twofold increase in 1987 dioxin.

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

Table 17-18. Analysis of Lupus Panel: MSK Parietal Antibody (Continued)

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | |
|--|--|----------------|
| Analysis Results for Log ₂ (1987 Dioxin + 1) | | |
| n | Adjusted Relative Risk (95% C.I.)^a | p-Value |
| 814 | 1.22 (0.93,1.60) | 0.140 |

^a Relative risk for a twofold increase in 1987 dioxin.

The unadjusted analysis for Model 3 revealed a marginally significant difference in the presence of the MSK parietal antibody among Ranch Hands in the low dioxin category and Comparisons (Table 17-18(e): p=0.082, Est. RR=1.68). The percentage of participants with the MSK parietal antibody present was 7.2 among Ranch Hands in the low dioxin category and 4.3 for Comparisons. After adjustment for covariates, the difference between Ranch Hands in the low dioxin category and Comparisons was nonsignificant (Table 17-18(f): p=0.192). All other Model 3 contrasts were nonsignificant (Table 17-18(e,f): p>0.17).

17.2.2.1.16 Lupus Panel: Rheumatoid Factor

All Model 1 unadjusted and adjusted contrasts examining the presence of a positive rheumatoid factor among Ranch Hands and Comparisons were nonsignificant (Table 17-19(a,b): p>0.16).

Table 17-19. Analysis of Lupus Panel: Rheumatoid Factor

| (a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED | | | | | |
|--|-------------------|--------------|---------------------------|--------------------------------------|----------------|
| Occupational Category | Group | n | Number (%) Present | Est. Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | <i>Ranch Hand</i> | <i>830</i> | <i>89 (10.7)</i> | <i>0.95 (0.72,1.27)</i> | <i>0.748</i> |
| | <i>Comparison</i> | <i>1,199</i> | <i>134 (11.2)</i> | | |
| Officer | Ranch Hand | 327 | 43 (13.2) | 1.13 (0.74,1.73) | 0.565 |
| | Comparison | 475 | 56 (11.8) | | |
| Enlisted Flyer | Ranch Hand | 142 | 19 (13.4) | 1.04 (0.54,2.00) | 0.904 |
| | Comparison | 178 | 23 (12.9) | | |
| Enlisted Groundcrew | Ranch Hand | 361 | 27 (7.5) | 0.72 (0.45,1.17) | 0.184 |
| | Comparison | 546 | 55 (10.1) | | |

| (b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED | | |
|--|--|----------------|
| Occupational Category | Adjusted Relative Risk (95% C.I.) | p-Value |
| <i>All</i> | <i>0.91 (0.69,1.22)</i> | <i>0.540</i> |
| Officer | 1.09 (0.71,1.68) | 0.692 |
| Enlisted Flyer | 0.98 (0.51,1.91) | 0.956 |
| Enlisted Groundcrew | 0.71 (0.44,1.15) | 0.167 |

Table 17-19. Analysis of Lupus Panel: Rheumatoid Factor (Continued)

| (c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED | | | | |
|---|----------|---------------------------|--|----------------|
| Initial Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (Initial Dioxin)^a | |
| Initial Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.)^b | p-Value |
| Low | 148 | 15 (10.1) | 0.75 (0.57,0.99) | 0.033 |
| Medium | 152 | 17 (11.2) | | |
| High | 153 | 10 (6.5) | | |

^a Adjusted for percent body fat at the time of the blood measurement of dioxin.

^b Relative risk for a twofold increase in initial dioxin.

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

| (d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED | | |
|--|--|----------------|
| Analysis Results for Log₂ (Initial Dioxin) | | |
| n | Adjusted Relative Risk (95% C.I.)^a | p-Value |
| 449 | 0.83 (0.60,1.14) | 0.233 |

^a Relative risk for a twofold increase in initial dioxin.

| (e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED | | | | |
|---|----------|---------------------------|---|----------------|
| Dioxin Category | n | Number (%) Present | Est. Relative Risk (95% C.I.)^{ab} | p-Value |
| Comparison | 1,164 | 130 (11.2) | | |
| Background RH | 371 | 46 (12.4) | 1.15 (0.80,1.65) | 0.458 |
| Low RH | 222 | 27 (12.2) | 1.10 (0.70,1.70) | 0.686 |
| High RH | 231 | 15 (6.5) | 0.54 (0.31,0.95) | 0.032 |
| Low plus High RH | 453 | 42 (9.3) | 0.77 (0.52,1.12) | 0.170 |

^a Relative risk and confidence interval relative to Comparisons.

^b Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 17-19. Analysis of Lupus Panel: Rheumatoid Factor (Continued)

| (f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED | | | |
|---|----------|--|----------------|
| Dioxin Category | n | Adjusted Relative Risk (95% C.I.)^a | p-Value |
| Comparison | 1,154 | | |
| Background RH | 365 | 1.04 (0.71,1.51) | 0.841 |
| Low RH | 220 | 1.03 (0.66,1.61) | 0.890 |
| High RH | 229 | 0.59 (0.33,1.04) | 0.068 |
| Low plus High RH | 449 | 0.77 (0.53,1.14) | 0.195 |

^a Relative risk and confidence interval relative to Comparisons.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.

Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.

High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

| (g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED | | | | |
|--|----------|---------------------------|---|----------------|
| 1987 Dioxin Category Summary Statistics | | | Analysis Results for Log₂ (1987 Dioxin + 1) | |
| 1987 Dioxin | n | Number (%) Present | Estimated Relative Risk (95% C.I.)^a | p-Value |
| Low | 281 | 36 (12.8) | 0.81 (0.69,0.96) | 0.010 |
| Medium | 271 | 33 (12.2) | | |
| High | 272 | 19 (7.0) | | |

^a Relative risk for a twofold increase in 1987 dioxin.

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

| (h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED | | | |
|---|--|--|----------------|
| Analysis Results for Log₂ (1987 Dioxin + 1) | | | |
| n | Adjusted Relative Risk (95% C.I.)^a | | p-Value |
| 814 | 0.86 (0.71,1.04) | | 0.122 |

^a Relative risk for a twofold increase in 1987 dioxin.

A significant inverse association between initial dioxin and the presence of a positive rheumatoid factor was found from the Model 2 unadjusted analysis (Table 17-19(c): p=0.033, Est. RR=0.75). After adjustment for covariates, the association became nonsignificant (Table 17-19(d): p=0.233).

The Model 3 unadjusted analysis displayed a significant difference in the percentage of positive rheumatoid factors among Ranch Hands in the high dioxin category (6.5%) and Comparisons (11.2%) (Table 17-19(e): p=0.032, Est. RR=0.54). After adjustment for covariates, the difference was marginally significant (Table 17-19(f): p=0.068, Adj. RR=0.59). All other unadjusted and adjusted Model 3 contrasts were nonsignificant (Table 17-19(e,f): p≥0.17).

A significant inverse association between the 1987 dioxin levels and the presence of a positive rheumatoid factor was found in the Model 4 unadjusted analysis (Table 17-19(g): $p=0.010$, Est. RR=0.81). After adjustment for covariates, the association was nonsignificant (Table 17-19(h): $p=0.122$).

17.3 DISCUSSION

Immunologic competence was assessed by a combination of laboratory assays on blood samples that examined lymphocyte surface markers on a randomized subset of the study population, immunoglobulin quantitation, and autoantibodies.

Evaluation of the human immune system is divided into two separate segments: humoral and cellular immunity. Circulating in the plasma phase of blood, the humoral segment consists of the immunoglobulins and complement proteins (complement C3 and C4 analysis presented in Chapter 13, Gastrointestinal Assessment). Some immunoglobulins (especially IgA) are prominent at exposed sites of the body (e.g., the mucosal surfaces of the mouth, pulmonary tract, and gastrointestinal tract), where direct contact with microorganisms is frequent. The serum immunoglobulins are secreted by plasma cells within the bone marrow through a process regulated in a sequence of events modulated by macrophages and memory lymphocytes. The immunoglobulins serve as a defense against bacterial infections, the bloodborne phase of viral infections, and in many other situations when microorganisms invade the body.

Quantitation of the immunoglobulins IgG, IgA, and IgM in serum gives an overall view of B cell integrity when related to the expected reference range values found in a normal, healthy population. Selective deficiency of one or more of these antibody classes, whether congenital or acquired, may be associated with increased susceptibility to infections (e.g., pneumonia). Congenital deficiencies are usually clinically evident early in life due to a large number of infections frequently resulting in death in childhood. Acquired deficiencies of immunoglobulins can occur in leukemias and lymphomas that invade the bone marrow later in adult life. Elevations of these immunoglobulins in a polyclonal pattern are frequently an indication of chronic infections (perhaps as compensation for the impairment of another segment of the immune response), of chronic inflammation such as in autoimmune disease, or of faulty regulation of B cell responses such as occurs in hepatic cirrhosis. Thus, measurement of immunoglobulins in serum yields clinical information relevant to past immunologic stimulation from infections, potential to defend the body against further infectious challenges, and the functional capacity of the liver in chronic disease.

Further evidence for the integrity of the immune system in aging individuals is the presence or absence of various autoantibodies. The autoantibodies measured in the lupus panel are considered to be abnormalities when present. Although autoantibodies often demonstrate an association with specific diseases that is useful in diagnosing and monitoring those diseases, sometimes the same autoantibodies can be found as isolated laboratory abnormalities in otherwise healthy individuals. In those cases, autoantibodies may be interpreted almost as renegade substances deriving from an aging and faltering immune system, and as such are markers for deterioration of the B cell regulatory process of immunity.

The second segment, cellular immunity, consists of both granulocytic and lymphocytic processes. Abnormalities of granulocytes can frequently be discerned from examination of the peripheral blood smear as part of the complete blood count. In addition, the medical history of individuals is usually sufficient to ascertain whether granulocyte deficiency is a consideration. Chapter 16, Hematologic Assessment, discusses the effect of dioxin on the components of these cells.

The total number of circulating lymphocytes (also called absolute number) provides information relative to the basic cellular quantity of cells present and available in the body for mounting an immune response. An increase in the total number of lymphocytes is observed in lymphocytic leukemias; it may also occur as a defensive immune response to some acute infections. Deficiency in the total number of lymphocytes may indicate susceptibility to infections with viruses or fungi. The total number of lymphocytes is usually decreased in malnutrition, often leading to infections in malnourished persons.

Examination of marker proteins on the surfaces of lymphocytes by flow cytometry is an excellent means of evaluating whether the regulatory interactions between the subpopulations of T cells, B cells, and monocytes are intact. An alteration in the percentages of any of these categories of cells can be considered presumptive evidence of an inability to recognize and destroy foreign infectious agents or tumor cells. The marker for total T cells was CD3+; the T cells were further broken down into the subpopulations of CD4+ (helper cells) and CD8+ (suppressor cells). The body's ability to respond to infectious challenges decreases in proportion to depression of the CD4+ count. This relation is particularly important in patients with AIDS because the HIV directly infects and destroys CD4+ lymphocytes, thereby incapacitating the immune system leading to infections with opportunistic organisms that normally would not cause infections in humans. The CD4+ count is also depressed by immunosuppressive medications such as cyclosporine, which are used to prevent rejection of organ transplants (e.g., kidney, heart). Immunosuppressed persons have a higher rate of malignancies, presumably in part because of diminished capacity of the immune system to search for and destroy tumor cells. The CD16+56+ markers are found on natural killer lymphocytes that provide a strong line of defense against growth of neoplasms through their action of destroying target cells by antibody-dependent, complement-mediated cytotoxicity. Changes in the mean number of CD16+56+ cells (natural killer cells) should not be over interpreted. Scientists know very little about the clinical significance of these cells; some authors suggest that these cells alter during times of stress. Occasionally, there has been a case report of patients who lack these cells. In general, the natural killer cell population is heterogeneous and the role of these cells in humans is unknown. CD20+ is a surface marker for B cells and gives an indication of the balance between cellular immunity and the ability to mount a B cell response with production of specific antibodies.

Interpretation of alterations in the relative amounts of B cells, T cells, their subsets, and monocytes is based on the expectation that all aspects of the immune system must be intact to prevent infections and to guard against development of tumors with unusual surface antigens. The antibodies specific for tumors can either help to destroy them by binding complement and lysing the cells or stabilize them if those antibodies attach to the tumor surface without binding complement, thereby blocking immune recognition and destruction of tumor cells. The T cells also have antigen receptors on their surfaces that similarly call into play the destructive power of the entire lymphocyte cell line in an antitumor attack. T cells stimulated by interleukin-2 have even greater capacity to attack and destroy foreign antigens and tumors by the other recognition factors such as antibodies and complement proteins.

The immunologic evaluation performed on AFHS participants went far beyond the usual medical examinations employed for general health assessments. As a test panel battery, this assessment provided an in-depth, broad review of immunologic parameters designed to detect abnormalities or variances that may or may not carry clinical import. In fact, the choice of all these sensitive laboratory tests may make it statistically possible to detect some subtle effect of dioxin on the immune system.

This thorough evaluation of the immune system did not reveal any relations between dioxin exposure and clinically overt disease, but unknown subclinical effects of dioxin on the immune system cannot be ruled out. Some individual elements showed statistical significance, although the magnitude of such relations was small and certainly not to be interpreted as conveying health risk. These included the following

associations with increasing dioxin level: a slight increase in CD3+ cells (T cells), a slight increase in CD4+ cells (helper T cells), a slight decrease in CD16+56+ cells (natural killer cells), and a slight increase in CD20+ cells (B cells). These combinations of results do not necessarily indicate a disorder, and the magnitude of each effect in itself is not considered clinically meaningful. The difference in the magnitude of absolute lymphocytes between the 1992 examination (the mean was approximately 1,940 cells/mm³) versus the 1997 examination (the mean was approximately 1,780 cells/mm³) was caused by an equipment upgrade from the Coulter STKR[®] in 1992 to the Coulter STKS[®] in 1997. The Coulter STKS[®] had a slightly lower reference range than the Coulter STKR[®].

In the 1997 study, approximately 50 percent of both Ranch Hand and Comparison participants exhibited positive results on the ANA test. This positive rate was much higher than expected for an adult male population. The ANA positive rate also was significantly higher in the 1997 study than in the 1992 study, when about 15 percent of both Ranch Hand and Comparison groups were positive. A shift in the sensitivity of detection for ANA may have occurred from the 1992 study to the 1997 study. In 1997, all ANA tests were read by the same dedicated technologist. For the last several months of the study, the tests also were backread by an expert reviewer who verified all positive results. This quality control procedure guaranteed that the technique for detection was consistent and accurate in the 1997 study. ANA is a screening test done at a particular dilution of serum, typically 1:40. Samples that screen positive are then titrated to endpoint (1:80, 1:160, etc.) and a pattern (e.g., homogeneous, speckled, nucleolar, centromere) is identified. Most laboratory clinicians screen at 1:40 and report results that are less than or equal to 1:160 as “indeterminate” or “borderline.” Borderline ANA test results rarely are clinically important (significant). The clinician decides whether the result is clinically important and whether to do follow-up tests for more specific antinuclear antibodies. Results of 1:320 or greater are considered positive; the higher the titer, the more likely it is to be clinically significant.

The screening dilution (1:40 in the AFHS) usually is determined by the laboratory to be that concentration at which 95 percent of normal individuals are negative. As humans age, it is well recognized that the percentage of normal asymptomatic individuals who screen positive increases. It is not practical to adjust screening dilutions by age; therefore, screening at a dilution of 1:40 is used for all individuals—regardless of their age—knowing that there will be more false positives as age increases. Clinicians usually take that into consideration when interpreting the low level positives and borderline results.

In the AFHS, the ANA test was scored as positive or negative. The percentage positive in the Comparison group is more than 5 percent, as it was in the last report, for two reasons: (1) it does not distinguish trivial positives from serious positives and (2) the population is getting older. Unfortunately, readers lacking knowledge of the test may interpret this as a Vietnam effect, when in fact the increase is more likely due to aging and lack of resolution of the degree of abnormality. In future studies, the degree of abnormality will be scored.

An inverse relation was found between dioxin exposure and the presence of autoantibodies against MSK smooth muscle. Other autoantibodies examined (ANA in the lupus panel and rheumatoid factor) did not show a relation with dioxin in the 1997 follow-up study, although they had previously done so in the 1992 follow-up examination. The Comparison group showed a rate of abnormal (positive) results for smooth muscle autoantibody that is expected in a general population. As in the 1992 follow-up study, the Ranch Hand group actually had a lower number of abnormal results for the smooth muscle autoantibody than did the Comparison group. This statistically negative association may indicate a highly sensitive but not clinically meaningful first indication of a generalized immune suppression, because a certain percentage of normal individuals should have been expected to test positive but did not. Clarification of the relevance of these findings to a hypothesis of dioxin-induced immune suppression will require longitudinal analysis of data from future physical examinations.

Serum IgA concentrations increased significantly with initial dioxin. IgA means were not significantly increased in Ranch Hand enlisted groundcrew or in the high dioxin category and IgA did not increase significantly with 1987 dioxin. Similar results were observed in 1992 and in 1987. In 1992, significant increases in IgA with initial dioxin were noted; there were no corresponding increases in Ranch Hand enlisted groundcrew or in the high dioxin category. IgA was not significantly related with 1987 dioxin. In 1987, IgA increased significantly with initial dioxin, but was not significantly increased in the high dioxin category; the Ranch Hand and Comparison IgA means were not significantly different and analyses restricted to enlisted groundcrew were not conducted. IgA was not measured in 1982 and 1985. These results, although significant, were small in magnitude and their clinical significance is unknown.

In many instances, statistical correlations existed between immunologic parameters and the covariates age, tobacco use, alcohol consumption, and exercise. Consequently, it is important to account for this potential source of variation between Ranch Hands and Comparisons. The analysis of covariate associations with immunologic variables yielded strong findings, especially with regard to current and lifetime cigarette smoking. Recent work has demonstrated the particular effect of tobacco use on the immune response (53–57). Current and lifetime alcohol use showed some mild associations, while physical activity was important with higher lymphocyte counts and populations of CD3+ cells (T cells), CD4+ cells (helper T cells), CD8+ cells (suppressor T cells), and CD20+ cells (B cells) in the more sedentary individuals.

In summary, these findings and the findings from past examinations do not provide evidence of a clinically meaningful dose-response effect for body burden of dioxin on parameters of immunologic assessment. The statistically significant relations emphasize the need for long-term evaluation.

17.4 SUMMARY

The immunologic assessment was based upon data gathered from laboratory collections. Associations with group (Model 1), initial dioxin (Model 2), categorized dioxin (Model 3), and 1987 dioxin levels (Model 4) were examined for each variable comprising the immunologic assessment.

17.4.1 Model 1: Group Analysis

Model 1 analyses revealed significant findings for both the unadjusted and adjusted analyses of CD16+56+ cell (natural killer cell) count and for the MSK smooth muscle antibody test. Each significant result was in the enlisted flyer occupational stratum. The mean CD16+56+ cell count was greater for Comparisons than for Ranch Hands, and a greater percentage of Comparisons had a smooth muscle antibody present than Ranch Hands. Marginally significant findings were found within the unadjusted examination of the CD16+56+ cell count when all occupations were combined, where the mean CD16+56+ cell count was greater for Comparisons than for Ranch Hands. This association was nonsignificant when adjusted for covariates. Among officers, a marginally significant difference in the percentage of the participants with the MSK mitochondrial antibody present was found in the adjusted analysis, where the antibody was more prevalent among Ranch Hands than among Comparisons. The CD3+ cell (T cell) count mean difference for enlisted groundcrew in the adjusted analysis was marginally significant. The CD3+ cell count mean was higher among Comparisons than Ranch Hands. Results for Model 1 analyses are summarized in Table 17-20.

Table 17-20. Summary of Group Analysis (Model 1) for Immunology Variables (Ranch Hands vs. Comparisons)

| Variable | UNADJUSTED | | | |
|--|------------|---------|----------------|---------------------|
| | All | Officer | Enlisted Flyer | Enlisted Groundcrew |
| Laboratory | | | | |
| CD3+ Cells (T Cells) (C) | ns | NS | ns | ns |
| CD4+ Cells (Helper T Cells) (C) | ns | NS | ns | ns |
| CD8+ Cells (Suppressor T Cells) (C) | ns | NS | ns | ns |
| CD16+56+ Cells (Natural Killer Cells) (C) | ns* | ns | -0.018 | ns |
| CD20+ Cells (B Cells) (C) | ns | NS | ns | ns |
| CD3+CD4+ Cells (Helper T Cells) (C) | ns | NS | ns | ns |
| Absolute Lymphocytes (C) | ns | NS | ns | ns |
| IgA (C) | ns | ns | NS | ns |
| IgG (C) | ns | ns | ns | ns |
| IgM (C) | ns | ns | ns | ns |
| Lupus Panel: ANA Test (D) | NS | ns | NS | NS |
| Lupus Panel: ANA Thyroid Microsomal Antibody (D) | NS | NS | ns | NS |
| Lupus Panel: MSK Smooth Muscle Antibody (D) | NS | NS | -0.040 | NS |
| Lupus Panel: MSK Mitochondrial Antibody (D) | NS | NS | ns | -- |
| Lupus Panel: MSK Parietal Antibody (D) | NS | NS | ns | ns |
| Lupus Panel: Rheumatoid Factor (D) | ns | NS | NS | ns |

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

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

C: Continuous analysis.

D: Discrete analysis.

--: Relative risk < 1.00 for discrete analysis; difference of means negative for continuous analysis.

--: Analysis not performed because of the sparse number of participants with the MSK mitochondrial antibody present.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

| Variable | ADJUSTED | | | |
|---|----------|---------|----------------|---------------------|
| | All | Officer | Enlisted Flyer | Enlisted Groundcrew |
| Laboratory | | | | |
| CD3+ Cells (T Cells) (C) | ns | NS | ns | ns* |
| CD4+ Cells (Helper T Cells) (C) | ns | NS | ns | ns |
| CD8+ Cells (Suppressor T Cells) (C) | ns | NS | ns | ns |
| CD16+56+ Cells (Natural Killer Cells) (C) | ns | ns | -0.011 | ns |
| CD20+ Cells (B Cells) (C) | ns | NS | ns | ns |
| CD3+CD4+ Cells (Helper T Cells) (C) | ns | NS | ns | ns |
| Absolute Lymphocytes (C) | ns | NS | ns | ns |

Table 17-20. Summary of Group Analysis (Model 1) for Immunology Variables (Ranch Hands vs. Comparisons) (Continued)

| Variable | ADJUSTED | | | |
|--|----------|---------|----------------|---------------------|
| | All | Officer | Enlisted Flyer | Enlisted Groundcrew |
| IgA (C) | ns | ns | NS | ns |
| IgG (C) | ns | ns | ns | ns |
| IgM (C) | ns | ns | ns | ns |
| Lupus Panel: ANA Test (D) | NS | ns | NS | NS |
| Lupus Panel: ANA Thyroid Microsomal Antibody (D) | NS | NS | ns | NS |
| Lupus Panel: MSK Smooth Muscle Antibody (D) | ns | NS | -0.045 | NS |
| Lupus Panel: MSK Mitochondrial Antibody (D) | NS | NS* | -- | -- |
| Lupus Panel: MSK Parietal Antibody (D) | NS | NS | ns | ns |
| Lupus Panel: Rheumatoid Factor (D) | ns | NS | ns | ns |

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

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

C: Continuous analysis.

D: Discrete analysis.

--: Relative risk < 1.00 for discrete analysis; difference of means negative for continuous analysis.

--: Analysis not performed because of the sparse number of participants with the MSK mitochondrial antibody present.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

17.4.2 Model 2: Initial Dioxin Analysis

The Model 2 analyses revealed a significant association between CD20+ cell (B cell) count and initial dioxin for the unadjusted analysis and a marginally significant association for the adjusted analysis. The CD20+ cell count increased as initial dioxin increased. The association between initial dioxin and the CD3+CD4+ cell (helper T cells) count was marginally significant in the adjusted analysis, and the association between initial dioxin and IgA was significant in the adjusted analysis. The CD3+CD4+ cell count and IgA increased as initial dioxin increased. The association between initial dioxin and the MSK smooth muscle antibody test was marginally significant in both the unadjusted and adjusted analyses. The association between initial dioxin and the rheumatoid factor was significant in the unadjusted analysis. For both the MSK smooth muscle antibody and the rheumatoid factor, the percentage of Ranch Hands with a positive reading decreased as initial dioxin increased. Results for Model 2 analyses are summarized in Table 17-21.

Table 17-21. Summary of Initial Dioxin Analysis (Model 2) for Immunology Variables (Ranch Hands Only)

| Variable | Unadjusted | Adjusted |
|--|------------|----------|
| Laboratory | | |
| CD3+ Cells (T Cells) (C) | NS | NS |
| CD4+ Cells (Helper T Cells) (C) | NS | NS |
| CD8+ Cells (Suppressor T Cells) (C) | NS | NS |
| CD16+56+ (Natural Killer Cells) Cells (C) | ns | ns |
| CD20+ Cells (B Cells) (C) | +0.024 | NS* |
| CD3+CD4+ Cells (Helper T Cells) (C) | NS | NS* |
| Absolute Lymphocytes (C) | NS | NS |
| IgA (C) | NS | +0.046 |
| IgG (C) | ns | ns |
| IgM (C) | NS | ns |
| Lupus Panel: ANA Test (D) | NS | NS |
| Lupus Panel: ANA Thyroid Microsomal Antibody (D) | ns | ns |
| Lupus Panel: MSK Smooth Muscle Antibody (D) | ns* | ns* |
| Lupus Panel: MSK Mitochondrial Antibody (D) | -0.034 | -0.049 |
| Lupus Panel: MSK Parietal Antibody (D) | ns | ns |
| Lupus Panel: Rheumatoid Factor (D) | -0.033 | ns |

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

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

C: Continuous analysis.

D: Discrete analysis.

+: Slope nonnegative for continuous analysis.

-: Relative risk < 1.00 for discrete analysis.

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

A capital “NS” denotes a relative risk of 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis. A lowercase “ns” denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

17.4.3 Model 3: Categorized Dioxin Analysis

Results for Model 3 analyses are summarized in Table 17-22. The analysis found a significantly higher CD16+56+ cell (natural killer cell) count mean among Comparisons than Ranch Hands in the high dioxin category in both the unadjusted and adjusted analyses. A marginally significant smaller percentage of Ranch Hands in the high dioxin category had the MSK smooth muscle antibody present than did Comparisons in the unadjusted analysis. This difference between Ranch Hands and Comparisons was significant when adjusted for covariates. A significantly smaller percentage of Ranch Hands in the high dioxin category had a positive rheumatoid factor than did Comparisons in the unadjusted analysis. This difference between Ranch Hands and Comparisons was marginally significant when adjusted for covariates. A marginally significant difference in the presence of the MSK parietal antibody among Ranch Hands in the low dioxin category and Comparisons was found in the unadjusted analysis. The

percentage of participants with the parietal antibody present was higher among Ranch Hands in the low dioxin category than among Comparisons. After adjustment for covariates, the results were nonsignificant.

Table 17-22. Summary of Categorized Dioxin Analysis (Model 3) for Immunology Variables (Ranch Hands vs. Comparisons)

| Variable | UNADJUSTED | | | |
|--|--|---------------------------------|----------------------------------|---|
| | Background Ranch Hands vs. Comparisons | Low Ranch Hands vs. Comparisons | High Ranch Hands vs. Comparisons | Low plus High Ranch Hands vs. Comparisons |
| Laboratory | | | | |
| CD3+ Cells (T Cells) (C) | ns | ns | ns | ns |
| CD4+ Cells (Helper T Cells) (C) | ns | ns | NS | ns |
| CD8+ Cells (Suppressor T Cells) (C) | ns | ns | ns | ns |
| CD16+56+ Cells (Natural Killer Cells) (C) | ns | NS | -0.028 | ns |
| CD20+ Cells (B Cells) (C) | ns | ns | NS | ns |
| CD3+CD4+ Cells (T Helper Cells) (C) | ns | ns | NS | ns |
| Absolute Lymphocytes (C) | NS | ns | NS | ns |
| IgA (C) | ns | ns | NS | NS |
| IgG (C) | ns | ns | ns | ns |
| IgM (C) | ns | ns | ns | ns |
| Lupus Panel: ANA Test (D) | NS | ns | NS | ns |
| Lupus Panel: ANA Thyroid Microsomal Antibody (D) | NS | NS | ns | ns |
| Lupus Panel: MSK Smooth Muscle Antibody (D) | NS | NS | ns* | ns |
| Lupus Panel: MSK Mitochondrial Antibody (D) | NS | NS | ns | NS |
| Lupus Panel: MSK Parietal Antibody (D) | ns | NS* | ns | NS |
| Lupus Panel: Rheumatoid Factor (D) | NS | NS | -0.032 | ns |

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

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

C: Continuous analysis.

D: Discrete analysis.

-: Relative risk < 1.00 for discrete analysis; difference of means negative for continuous analysis.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 17-22. Summary of Categorized Dioxin Analysis (Model 3) for Immunology Variables (Ranch Hands vs. Comparisons) (Continued)

| Variable | ADJUSTED | | | |
|--|--|---------------------------------|----------------------------------|---|
| | Background Ranch Hands vs. Comparisons | Low Ranch Hands vs. Comparisons | High Ranch Hands vs. Comparisons | Low plus High Ranch Hands vs. Comparisons |
| Laboratory | | | | |
| CD3+ Cells (T Cells) (C) | ns | ns | ns | ns |
| CD4+ Cells (Helper T Cells) (C) | ns | ns | ns | ns |
| CD8+ Cells (Suppressor T Cells) (C) | ns | ns | ns | ns |
| CD16+56+ Cells (Natural Killer Cells) (C) | ns | NS | -0.046 | ns |
| CD20+ Cells (B Cells) (C) | NS | ns | ns | ns |
| CD3+CD4+ Cells (Helper T Cells) (C) | ns | ns | ns | ns |
| Absolute Lymphocytes (C) | NS | ns | ns | ns |
| IgA (C) | ns | ns | NS | NS |
| IgG (C) | ns | ns | ns | ns |
| IgM (C) | ns | ns | ns | ns |
| Lupus Panel: ANA Test (D) | NS | ns | NS | ns |
| Lupus Panel: ANA Thyroid Microsomal Antibody (D) | NS | NS | ns | ns |
| Lupus Panel: MSK Smooth Muscle Antibody (D) | NS | NS | -0.048 | ns |
| Lupus Panel: MSK Mitochondrial Antibody (D) | NS | NS | -- | -- |
| Lupus Panel: MSK Parietal Antibody (D) | ns | NS | ns | NS |
| Lupus Panel: Rheumatoid Factor (D) | NS | NS | ns* | ns |

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

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

C: Continuous analysis.

D: Discrete analysis.

--: Relative risk < 1.00 for discrete analysis; difference of means negative for continuous analysis.

--: Analysis not performed because of the sparse number of participants with the MSK mitochondrial antibody present.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

17.4.4 Model 4: 1987 Dioxin Level Analysis

The Model 4 adjusted analyses uncovered significant associations between 1987 dioxin levels and CD3+ cell (T cell) count, CD4+ cell (helper T cell) count, and CD3+CD4+ cell (helper T cell) count. The cell counts increased as 1987 dioxin increased. Marginally significant associations with 1987 dioxin levels were found in the unadjusted analyses of IgA and MSK smooth muscle antibody. The IgA association showed an increase in IgA levels as 1987 dioxin increased. The percentage of Ranch Hands with a smooth muscle antibody present decreased as 1987 dioxin levels increased. The unadjusted analyses of the rheumatoid factor were significant, showing a decrease in the percentage of participants with a rheumatoid factor present as 1987 dioxin levels increased. All the significant or marginally significant

associations found in the unadjusted analyses were nonsignificant in the adjusted analyses. Results for Model 4 analyses are summarized in Table 17-23.

Table 17-23. Summary of 1987 Dioxin Analysis (Model 4) for Immunology Variables (Ranch Hands Only)

| Variable | Unadjusted | Adjusted |
|--|------------|----------|
| Laboratory | | |
| CD3+ Cells (T Cells) (C) | NS | +0.046 |
| CD4+ Cells (Helper T Cells) (C) | NS | +0.033 |
| CD8+ Cells (Suppressor T Cells) (C) | NS | NS |
| CD16+56+ Cells (Natural Killer Cells) (C) | NS | ns |
| CD20+ Cells (B Cells) (C) | NS | NS |
| CD3+CD4+ (Helper T Cells) Cells (C) | NS | +0.025 |
| Absolute Lymphocytes (C) | NS | NS |
| IgA (C) | NS* | NS |
| IgG (C) | NS | ns |
| IgM (C) | ns | ns |
| Lupus Panel: ANA Test (D) | ns | ns |
| Lupus Panel: ANA Thyroid Microsomal Antibody (D) | ns | ns |
| Lupus Panel: MSK Smooth Muscle Antibody (D) | ns* | ns |
| Lupus Panel: MSK Mitochondrial Antibody (D) | ns | ns |
| Lupus Panel: MSK Parietal Antibody (D) | NS | NS |
| Lupus Panel: Rheumatoid Factor (D) | -0.010 | ns |

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

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

C: Continuous analysis.

D: Discrete analysis.

+: Slope nonnegative for continuous analysis.

-: Relative risk < 1.00 for discrete analysis.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

17.5 CONCLUSION

The immunologic assessment was based upon laboratory data on six lymphocyte cell surface markers, absolute lymphocyte counts, three quantitative immunoglobulins, and six measurements from an autoantibody panel. The six cell marker measurements were carried out on a random sample of approximately 40 percent of the participants because of the complexity of the assay and the expense of the tests.

Group analyses revealed significant findings for the adjusted analyses of CD16+56+ cell (natural killer cell) count and for the MSK smooth muscle antibody test in enlisted flyers. Among enlisted flyers, the mean CD16+56+ cell count was greater for Comparisons than for Ranch Hands, and a greater percentage of Comparisons than Ranch Hands had a smooth muscle antibody present. For these analyses the

magnitude of the mean differences was small; therefore, the clinical importance of these findings is unknown.

Consistent with the previous two physical examinations, the mean serum concentration of IgA increased significantly with initial dioxin, but was not significantly increased in enlisted groundcrew or the high dioxin category; IgA did not increase significantly with 1987 dioxin. The IgA results, although significant, were small in magnitude and their clinical significance is unknown.

When comparing categorized dioxin levels between Ranch Hands and Comparisons, a significantly higher CD16+56+ cell count mean was observed among Comparisons than among Ranch Hands in the high dioxin category. Analyses revealed significant associations between 1987 dioxin levels and CD3+ cell (T cell) count, CD4+ cell (helper T cell) count, and CD3+CD4+ cell (helper T cell) count. The cell counts increased as 1987 dioxin increased.

In summary, these findings do not provide evidence of a biologically meaningful relation between body burden of dioxin and parameters of immunologic assessment. The statistically significant relations point out the need for long-term evaluation.

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