CHAPTER 19
IMMUNOLOGIC ASSESSMENT

INTRODUCTION

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 (TCDD, or dioxin) has proven to be the most toxic. Since the early 1970s, when TCDD was shown to cause marked involution of the thymus gland in numerous experimental animals (1-4), an extensive body of literature pertinent to TCDD-induced immunotoxicity has been summarized in the recent comprehensive review article by Holsapple and colleagues (5). In laboratory animals, TCDD has proven to have a wide range of toxic effects on all components of the immune system including the following:

- Compromised cell mediated (6,7) and humoral (8-10) immune function
- Impaired myelo-(11,12) and lymphoproliferative (11,13-15) responses
- Suppressed complement activity (16,17)
- Compromised host resistance to bacterial (8,11,17-19), parasitic (20), and viral (19,21) infections.

In an attempt to provide data more relevant to humans, two laboratories have conducted experiments into the effects of TCDD on numerous immunologic indices in marmoset (22-24) and rhesus monkeys (25). These studies, carried out in vitro in lymphocyte cell cultures and in vivo with single dose injections of TCDD in various concentrations, have yielded inconsistent results that in many cases do not fit a typical dose-response pattern. The relevance of these acute phase studies to the long-term occupational exposure more typical in humans remains to be proven. In none of the in vivo studies have the animals shown evidence of overt illness.

Much of the past and current basic research in laboratory animals has focused on the importance of the aryl hydrocarbon (Ah) receptor in some but not all manifestations of TCDD toxicity including suppressed humoral (10,26-32) and cellular (33,34) responses and impaired complement activity (35). Numerous additional studies have demonstrated that TCDD effects can occur independent of the presence of the Ah receptor (27,28,30-32,36-39). Although the Ah receptor has been defined in several human tissues (see references 40-45 in Chapter 9, General Health) the relevance of these observations to TCDD toxicity in humans remains controversial. Two comprehensive reviews have summarized the voluminous literature related to the mechanisms of TCDD immunotoxicity and the role of the Ah receptor (40,41). In contrast to the active research in animals, relatively few studies have been published describing immune system effects of TCDD in humans and from these studies

no consistent evidence for immunotoxicity has been found. Most reports have been based on populations exposed to TCDD as a consequence of industrial accidents, environmental contamination, or military service in Vietnam.

In early reports on a population at risk from soil contamination in Times Beach, Missouri, abnormalities in several indices of immune function were documented including impaired delayed hypersensitivity by skin testing and nonsignificant variations in several peripheral lymphocyte subsets and ratios (42,43). However, followup examinations of the same subjects found no differences between those exposed and the controls (44,45).

Reports of examinations conducted on individuals exposed in industrial explosions in England (46) and Seveso, Italy (47) noted minor variations in several immunologic indices, but none were of apparent clinical significance.

Finally, in the most recent report of the Air Force Health Study (AFHS) (48), in which immunologic indices were examined in relation to the current body burden of dioxin, a statistically significant increase in the IgA globulin fraction was noted in the Ranch Hand cohort. Although of uncertain significance, this finding is of interest given a report of a laboratory animal study (49) that documented a selective increase in the IgA fraction upon exposure to a single injection of TCDD. There were no other significant differences between the Ranch Hand and Comparison cohorts.

Summary of Previous Analyses of the Air Force Health Study

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 T_{11}, CD3 or T_3, CD4 or T_4, CD8 or T_8, CD20 or B, the CD4-CD8 or T_4-T_8 ratio, and the total lymphocyte count (TLC) showed no significant group differences. However, increased 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 a herbicide effect. Smoking was associated with a significant increase in the marker cells CD2, CD3,

CD4, and CD8, and in the TLC, with a concomitant increase in lymphocytic response to pokeweed mitogen (PWM).

1985 Followup Study Summary Results

The 1985 AFHS physical examination placed more emphasis on the immunologic assessment than did the 1982 Baseline 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, CD4 cells, CD8 cells, CD20 or B cells, CD14 cells or 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 (in pack-years), current alcohol use, or lifetime alcohol use (in drink-years). 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 a detriment 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 were usually 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 followup 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.

1987 Followup Study Summary Results

For the assessment of the 1987 immunologic examination data, composite skin reaction test results and various laboratory examination measurements from cell surface marker studies, three groups of functional stimulation tests, and quantitative immunoglobulins 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 significance of these findings is not apparent and does not point to any known clinical endpoints. In general, the immunologic assessment revealed no medically important differences between Ranch Hands and Comparisons.

Serum Dioxin Analysis of 1987 Followup 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 displaying 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 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 significant indicators reflecting a relationship between the current body burden of dioxin or the extrapolated initial exposure and immune function were found. Similar to elevated erythrocyte sedimentation rates (in the General Health Assessment) and increased white blood cell and platelet counts (in the Hematologic Assessment), increased IgA levels could represent a chronic inflammatory response to dioxin exposure.

Parameters for the Immunologic Assessment

Dependent Variables

Data from the physical examination, the Scripps Clinic and Research Foundation (SCRF) laboratory, and the Scripps Immunology Reference Laboratory (SIRL) were used in the Immunologic Assessment. The skin testing, immunoglobulin studies, and lupus panel tests were examined for all participants, whereas the cell surface marker studies and total lymphocyte count (TLC) investigations 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.

Physical Examination Data

Physical examination data concerning the skin tests were used to evaluate immunologic function. A composite skin test diagnosis variable was constructed based on the responses to four separate antigens injected intradermally to measure antigen reactivity or sensitivity. This composite skin test variable was analyzed as a discrete, dichotomous variable; each participant was considered possibly abnormal or normal based on his skin reactivity to the antigens *Candida albicans*, mumps, Trichophyton, and staph-phage lysate. The response to each antigen was scored positive (normal) if the maximum diameter of the resulting 48-hour induration was greater than or equal to 5 millimeters (mm), which indicates intact cell-mediated immunity. If none of the four antigen responses was positive, the composite skin test diagnosis was scored possibly abnormal. If one or more of the four antigen responses were positive, the composite skin test was considered normal.

Participants who were taking anti-inflammatory medication (except aspirin) or immunosuppressant medication at the time of the 1992 physical examination, participants who recently received x ray treatment or chemotherapy for cancer (reported in the 1992 questionnaire and verified by medical records review), and participants who tested positive for HIV were excluded from all analyses of skin test data.

Laboratory Examination Data

From the SCRF and SIRL immunologic tests, the results of cell surface marker studies, TLC, quantitative immunoglobulins, and a lupus panel were analyzed. Table 19-1 presents the immunologic parameters evaluated and describes their medical importance. Continuous data were evaluated statistically to determine whether the natural logarithm scale was more

Table 19-1.
Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
Skin Tests		
Candida Mumps Trichophyton Staph-phage lysate	Skin testing measures in vivo hypersensitivity responses to antigens of bacteria, fungi, and a virus to which most persons have previously been exposed. The skin reaction to intradermal injection of these antigens indicates integrity of T-cell memory and ability of effector cells to mount a response.	Antigen reactivity or sensitivity. Lack of response to all antigens indicates anergy that may occur in overwhelming infections, widespread malignancy, immunosuppression, or malnutrition.
Cell Surface Marker Studies		
CD3	Pan T-cell marker (similar to CD2) in previous study cycle). 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 due to direct effects of malignancy (e.g., lymphoma), to AIDS, or to chemotherapy. Increase may occur in lymphoproliferative disorders or in some infections.
CD4 (Lue3a+b)	Measures T cells that exhibit helper/inducer phenotype. CD4 cells initiate an immune response to processed antigens.	Markedly decreased in AIDS due to HIV infection of CD4+ cells; increased in autoimmune diseases.
CD5	Marker expressed by T cells; also found on subpopulation of B cells.	B-cell type of chronic lymphocytic leukemia expresses CD5; lymphocytes involved in autoimmune disease frequently express CD5.
CD8 (OKT8)	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.
CD14 (LeuM3)	Measures mature monocytes in peripheral blood. Monocytes take up and process foreign antigens for presentation to CD4+ cells.	Increases with inflammation of many etiologies.
CD16+56	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.

Table 19-1. (Continued)
Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
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.
CD25 (IL-2 Receptor)	Present on activated T cells; absent on normal peripheral blood lymphocytes, monocytes, and granulocytes. Stimulation with IL-2 induces more IL-2 Receptor synthesis in activated T cells (positive feedback).	Increased in lymphoproliferative disorders. Also increased with any immune activation (viral infection, organ transplant rejection).
CD4-CD8 Ratio	Measures proportional difference between CD4+ cell populations and CD8+ cell populations. Reflects balance between up regulation and down regulation of T cells.	Decreased in immunodeficiencies and viral illnesses. AIDS causes very low ratio, as does immunosuppression with cyclosporine.
Double Labelled Cells (cells that express both markers)		
CD3 with CD25	More refined measurement of activated T cells to avoid possible (minor) inclusion of other cell types expressing CD25.	Same as CD25.
CD5 with CD20	T cell marker (CD5) with B cell marker (CD20) on same lymphocytes indicates abnormal cell subpopulation.	These doubly positive cells occur as a major population in chronic lymphocytic leukemia; as a minor population, they can indicate lymphocytes responsible for autoimmune processes.
CD4 with CD8	Normally these markers do not occur on the same cells.	Doubly positive cells indicate primitive lymphocytes suggesting abnormal T cell clone or leukemia.
CD3 with (CD16 + CD56)	Normally these markers do not occur on the same cells.	Same as CD16 plus CD56.
Total Lymphocyte Count	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 19-1. (Continued)
Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
Immunoglobulins 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).
Lupus Panel	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 also may 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 significant autoantibodies that occur in systemic rheumatologic diseases; all positives were further tested by confirmatory assays for specific autoantibodies against: DNA, Sm, RNP, SS-A, SS-B.	Positive result suggests possible rheumatologic disease; likelihood increases with number of different positive autoantibodies.
Thyroid Microsomal Antibody	Measures autoantibodies against thyroid.	Present in autoimmune thyroiditis.
MSK Smooth Muscle Antibody	MSK indicates the tissues used in the assay (mouse stomach and 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 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.

Table 19-1. (Continued)
Medical Significance of the Immunologic Data

Immunologic Measure	Rationale of the Measurement	Disease/Syndrome/Condition Endpoint
B Cell Clones Detected by Serum Protein Electrophoresis	Detection of monoclonal immunoglobulins by serum protein electrophoresis. Normal immunoglobulins are polyclonal with no predominant single clone. All positive results were further tested for heavy chain type (G, A, M) and light chain type (kappa, lambda).	Large amounts of monoclonal immunoglobulins are present in multiple myeloma and other lymphoproliferative disorders; also can occur in smaller amounts in aging or dysregulated immune systems.
Other Antibodies	May be detected incidentally in performance of the above assays, may not be clinically significant except as indicator of immune system aging or dysfunction.	
Summary Index	General measure of the integrity of the immune system, specifically as it affects B cells.	

appropriate to use with the statistical procedure(s) than the original scale. Participants who were taking anti-inflammatory medication (except aspirin) or immunosuppressant medication at the time of the 1992 physical examination, participants who had recently received x ray treatment or chemotherapy for cancer, and participants who tested positive for HIV were excluded from all analyses of the laboratory data.

Cell Surface Marker (Phenotypic) Studies—Quantification of the different cell populations was carried out with the use of reagent mouse monoclonal antibodies. Eight cell surface markers, one ratio of cell markers, and four double-labelled cell surface markers were analyzed in the statistical evaluation of the immunologic system. The unit of measurement (for all variables except the ratio) was cells/mm^3.

A substantial number of participants had measurements of 0 cells/mm^3 for the double-labelled cell surface markers CD5 with CD20, CD4 with CD8, and CD3 with CD16+56. The distribution of these double labelled cell surface markers were skewed, suggesting the need for a logarithmic transformation. Consequently two sets of analyses were done on each variable. Analyses were performed on the nonzero values in their continuous form incorporating a logarithmic transformation. A second analysis was done on each variable, relating the percentage of zero measurements to the estimate of exposure.

Total Lymphocyte Count (TLC)—The TLC indicates the density of lymphocytes in the blood. Lymphocytes recognize and destroy bacteria, fungi, viruses, and other foreign bodies. Statistical analysis was performed on TLC, as measured in cells/mm^3.

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

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 clinical significance. 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. Positive results are expressed as:
  - Titer (e.g., 1:40, 1:160)
  - Pattern (e.g., speckled, homogeneous, centromere, nucleolar, other ANA).

If the ANA was negative, no further specific antibody assays were performed. If the ANA was positive, the following major specific antibody measurements were performed:
- DNA
- Sm
- RNP
- SS-A
- SS-B.

- **Mouse stomach kidney (MSK) section stain** for the following specific autoantibodies:
  - Smooth muscle
  - Mitochondrial
  - Parietal cell
  - Other MSK.

- **Thyroid microsomal antibody**

- **Rheumatoid factor.**

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

Statistical analyses were performed on the ANA, MSK smooth muscle antibody, MSK mitochondrial antibody, MSK parietal cell antibody, thyroid microsomal antibody, rheumatoid factor, B-cell clones detected by serum protein electrophoresis, and other ANA and MSK antibodies, with the response to these tests scored as present or absent. The B-cell clones as detected by serum electrophoresis are a composite of 11 subtests and are considered present if any bands from the subtests are present. Statistical analyses also were performed on a lupus panel summary index, which was constructed from the eight individual tests and scored as "abnormal" if any of the eight individual tests were abnormal and "normal" if all eight tests were normal.

The test for B-cell clones performed by high resolution electrophoresis and immunofixation on serum is one additional measure of B-cell abnormality. High resolution electrophoresis for detection of monoclonal bands is not formally part of the lupus panel because such antibody bands are not necessarily autoantibodies. However, both autoantibodies and monoclonal bands are evidence for derangement of the B-cell portion of the immune system. For that reason, it is appropriate to include the B-cell clone test results with the lupus panel autoantibody results in a composite summary index of B-cell abnormalities.

Covariates

Covariates used in the immunologic evaluation for adjusted statistical analyses include 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). Further, batch-to-batch (examination group) variation also was used as a covariate for the cells surface maker (phenotypic) studies and TLC. Study participants who began their physical examination on the same day form a batch.

Lifetime alcohol history was based on self-reported information from the 1992 questionnaire and combined with similar information gathered at the 1987 followup. The respondent's average daily alcohol consumption was determined for various drinking stages throughout his lifetime, and an estimate of the corresponding total number of drink-years (1 drink-year is the equivalent of drinking 1.5 ounces of 80-proof alcoholic beverage per day for 1 year) was derived. The current alcohol covariate was based on the average drinks per day for the month prior to completing the questionnaire.

Current cigarette smoking and lifetime cigarette smoking history were based on self-reported questionnaire data. For lifetime cigarette smoking history, the respondent's average smoking was estimated over his lifetime, assuming 365 packs of cigarettes equal 1 pack-year.

A series of questions concerning exercise patterns in the past 2 weeks were added to the AFHS and incorporated in the 1992 questionnaire. The participants were asked questions on frequency, average duration per frequency, and increase of heart rate or breathing for over 20 different activities. The answers to these questions were used and combined to determine an index of physical activity incorporating duration and intensity (50,51), and this covariate was used in adjusted statistical analyses.

Statistical Methods

Chapter 7, Statistical Methods, describes most of the basic statistical methods used in the Immunologic Assessment. For both the 1985 and the 1987 studies, large variation was expected from batch variability. Because of the variation, this covariate was generally incorporated into the unadjusted and the adjusted models of the respective Immunologic Assessments for the 1985 and 1987 studies. For the analyses of the cell surface markers and TLC, the batch-to-batch covariate was subject to a prescreening procedure to determine whether the unadjusted and adjusted models should incorporate this covariate. The prescreening was performed because of the reduced sample sizes available for the stepwise modeling procedure applied to those models involving only the Ranch Hands. In addition, the batch-to-batch covariate absorbs many of the available degrees of freedom if routinely forced into a particular analysis model.

To address the issues regarding reduced sample sizes and decreased degrees of freedom, a main effects prescreening model with the following terms was used for the cell surface markers and TLC: group, batch-to-batch variation, age, race, occupation, current alcohol use, lifetime alcohol history, current cigarette smoking, lifetime cigarette smoking history, and exercise history index. The models were used to evaluate the significance of the batch-to-batch covariate using the data from the group analysis (the largest data set of the 6 models). As a result of that analysis, the batch-to-batch covariate was used for the unadjusted and adjusted analyses of the following cell surface markers: CD3, CD4, CD5,

CD14, CD16+56, CD25, CD3 with CD25, CD5 with CD20, CD3 with CD16+56, and TLC. Batch-to-batch variation was not used in the unadjusted and adjusted analyses of CD8, CD20, CD4-CD8 ratio, and CD4 with CD8.

Table 19-2 summarizes the statistical analyses performed for the analysis of the Immunologic Assessment. The first part of the table describes the dependent variables analyzed. The second part of the table further describes the candidate covariates examined. Abbreviations used in the body of the table are defined at the end of the table. Some participants were excluded from the immunologic evaluation as stated previously, and some dependent variable and covariate data were missing for other participants. Table 19-3 summarizes the number of participants excluded for medical reasons and the number of participants with missing data. Variables used to evaluate skin, immunologic testing, and the lupus panel tests are detailed separately in this table, because different subsets of participants received these types of tests.

Analyses of data collected at the 1987 followup study indicated that dioxin was associated with military occupation. In general, enlisted personnel had higher levels of dioxin than officers, with enlisted groundcrew having higher levels than enlisted flyers. Consequently, adjustment for military occupation in statistical models using dioxin as a measure of exposure may improperly mask an actual dioxin effect. However, occupation also can be a surrogate for socioeconomic effects. Failure to adjust for occupation could overlook important risk factors related to lifestyle. If occupation was found to be significantly associated with a dependent variable in the 1992 followup analyses and was retained in the final statistical models using dioxin as a measure of exposure, the dioxin effect was evaluated in the context of two models. Analyses were performed with and without occupation in the final models to investigate whether conclusions regarding the association between the health endpoint and dioxin differed.

The results of the analyses without occupation are presented in Appendix O-3 and are only discussed in the text if the level of significance differs from the original final adjusted model (significant versus nonsignificant).

Longitudinal Analyses

Longitudinal analyses were performed on the CD4-CD8 ratio using the data collected for the 1985 and 1992 examinations to assess the association between exposure and the change in this ratio between the two examinations. See Chapter 7, Statistical Methods, for a further discussion of methods used in the longitudinal analyses.

Table 19-2.
Statistical Analyses for the Immunologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Composite Skin Test Diagnosis (based on length of four skin test antigen induration measurements)	PE	D	Possibly Abnormal: 0/4 ≥5 mm Normal: ≥1/4 ≥5 mm	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
CD3 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
CD4 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM
CD5 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM
CD8 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM
CD14 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
CD16+56 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
CD20 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM
CD25 Cells (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM

Table 19-2. (Continued)
Statistical Analyses for the Immunologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
CD4-C8 Ratio	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM,TT A:GLM L:GLM,TT
Double Labelled Cells: CD3 with CD25 (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
Double Labelled Cells: CD5 with CD20 (cells/mm^3)	LAB	D/C	Zero Nonzero	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:LR,CS, GLM,TT A:LR,GLM
Double Labelled Cells: CD4 with CD8 (cells/mm^3)	LAB	D/C	Zero Nonzero	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:LR,CS, GLM,TT A:LR,GLM
Double Labelled Cells: CD3 with CD16+56 (cells/mm^3)	LAB	D/C	Zero Nonzero	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:LR,CS, GLM,TT A:LR,GLM
Total Lymphocyte Count (TLC) (cells/mm^3)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT,BATCH	U:GLM A:GLM
IgA (mg/dl)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:GLM A:GLM
IgG (mg/dl)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:GLM A:GLM
IgM (mg/dl)	LAB	C	--	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:GLM A:GLM
Lupus Panel: ANA Test	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR

Table 19-2. (Continued)
Statistical Analyses for the Immunologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Lupus Panel: ANA Thyroid Microsomal Antibody	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: MSK Smooth Muscle Antibody	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: MSK Mitochondrial Antibody	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: MSK Parietal Antibody	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: Rheumatoid Factor	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: Other Antibodies (ANA and MSK)	LAB	D	Present Absent	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR
Lupus Panel: Summary Index	LAB	D	Abnormal Normal	AGE,RACE,OCC, CSMOK,PACKYR, ALC,DRKYR, PHYACT	U:LR,CS A:LR

Table 19-2. (Continued)
Statistical Analyses for the Immunologic Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥ 1942 Born < 1942
Race (RACE)	MIL	D	Black Non-Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Current Cigarette Smoking (CSMOK) (cigarettes/day)	Q-SR	D/C	0-Never 0-Former >0-20 >20
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	D/C	0 >0-10 >10
Current Alcohol Use (ALC) (drinks/day)	Q-SR	D/C	0-1 >1-4 >4
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	D/C	0 >0-40 >40
Physical Activity Index (PHYACT) (kcal/kg/day)	Q-SR	D	Sedentary: <1.45 Moderate: 1.45-<2.95 Very Active: ≥2.95
Batch-to-Batch (BATCH)	LAB	D	1, 2, 3, ... 81

Abbreviations

Data Source:
- LAB = 1992 SCRF laboratory and SIRL results
- MIL = Air Force Military Records
- PE = 1992 physical examination
- Q-SR = Health questionnaires (self-reported)

Data Form:
- D = Discrete analysis only
- C = Continuous analysis only
- D/C = Discrete and continuous analyses for dependent variables; appropriate form for analysis (either discrete or continuous) for covariates

Statistical Analyses:
- U = Unadjusted analyses
- A = Adjusted analyses
- L = Longitudinal analyses

Table 19-3.
Number of Participants with Missing Data for, or Excluded from, the Immunologic Assessment

Variable	Variable Use	Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
		Ranch Hand	Comparison	Initial	Current	Ranch Hand	Comparison
Skin Test Analysis[a]							
Composite Skin Test Diagnosis	DEP	20	46	7	17	17	32
Chemotherapy or X Ray Treatment	EXC	2	4	2	2	2	3
Anti-Inflammatory or Immunosuppressant Medication	EXC	11	11	5	11	11	8
HIV Positive	EXC	3	1	2	3	3	1
Immunologic Test Analyses[b]							
CD3 Cells	DEP	1	0	1	1	1	0
CD4 Cells	DEP	1	0	1	1	1	0
CD5 Cells	DEP	1	0	1	1	1	0
CD8 Cells	DEP	1	0	1	1	1	0
CD14 Cells	DEP	1	0	1	1	1	0
CD16+56 Cells	DEP	1	0	1	1	1	0
CD20 Cells	DEP	1	0	1	1	1	0
CD25 Cells	DEP	1	0	1	1	1	0
CD4-CD8 Ratio	DEP	1	0	1	1	1	0
Double Labelled Cells: CD3 with CD25	DEP	1	0	1	1	1	0
Double Labelled Cells: CD5 with CD20	DEP	1	0	1	1	1	0
Double Labelled Cells: CD4 with CD8	DEP	1	0	1	1	1	0
Double Labelled Cells: CD3 with CD16+56	DEP	1	0	1	1	1	0
Total Lymphocyte Count	DEP	1	0	1	1	1	0

Table 19-3. (Continued)
Number of Participants with Missing Data for, or Excluded from, the Immunologic Assessment

Variable	Variable Use	Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
		Ranch Hand	Comparison	Initial	Current	Ranch Hand	Comparison
Chemotherapy or X Ray Treatment	EXC	1	3	0	1	1	3
Anti-Inflammatory or Immunosuppressant Medication	EXC	4	5	3	4	4	5
HIV Positive	EXC	0	1	0	0	0	1
Lupus Panel and Quantitative Immunoglobins[a]							
Lupus Panel: ANA Test	DEP	0	1	0	0	0	0
Lupus Panel: Thyroid Microsomal Antibody	DEP	0	1	0	0	0	0
Lupus Panel: MSK Smooth Muscle Antibody	DEP	0	1	0	0	0	0
Lupus Panel: Mitochondrial Antibody	DEP	0	1	0	0	0	0
Lupus Panel: MSK Parietal Antibody	DEP	0	1	0	0	0	0
Lupus Panel: Rheumatoid Factor	DEP	0	1	0	0	0	0
Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis	DEP	0	1	0	0	0	0
Lupus Panel: Other Antibodies	DEP	4	4	2	4	4	3
Lupus Panel: Summary Index	DEP	3	2	2	3	3	1
IgG	DEP	0	1	0	0	0	0
IgA	DEP	0	1	0	0	0	0
IgM	DEP	0	1	0	0	0	0

Table 19-3. (Continued)
Number of Participants with Missing Data for, or Excluded from, the Immunologic Assessment

Variable	Variable Use	Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
		Ranch Hand	Comparison	Initial	Current	Ranch Hand	Comparison
Chemotherapy or X Ray Treatment	EXC	2	4	2	2	2	3
Anti-Inflammatory or Immunosuppressant Medication	EXC	11	11	5	11	11	8
HIV Positive	EXC	3	1	2	3	3	1
Covariates							
Current Cigarette Smoking	COV	0	2	0	0	0	2
Lifetime Cigarette Smoking History	COV	1	2	0	1	1	2
Current Alcohol Use	COV	10	18	7	9	9	16
Lifetime Alcohol History	COV	22	21	13	20	20	18
Physical Activity Index	COV	0	2	0	0	0	2

[a]Performed on 952 Ranch Hands and 1,281 Comparisons.
[b]Performed on 373 Ranch Hands and 491 Comparisons.

Abbreviations: DEP = Dependent variable (missing data).
COV = Covariate (missing data).
EXC = Exclusion.

One Ranch Hand missing total lipids for current dioxin.

RESULTS

Dependent Variable-Covariate Associations

Appendix Table O-1-1 presents the results of the following tests of association between immunology variables and covariates.

The composite skin test variable was based on the response to four separate antigens injected intradermally to measure antigen reactivity or sensitivity increased significantly with age ($p=0.014$) and lifetime cigarette smoking history ($p=0.014$). Non-Black participants had a significantly higher percentage of abnormal composite skin test results than Black participants ($p=0.048$).

The cell surface marker analysis of CD3 cells showed that the number of CD3 cells decreased with age ($p=0.045$) and increased with current cigarette smoking ($p<0.001$) and lifetime cigarette smoking history ($p<0.001$). The number of CD3 cells were higher for enlisted flyers and enlisted groundcrew than for officers ($p=0.030$).

Similarly, analysis of CD4 cells revealed that the number of CD4 cells decreased with age ($p=0.002$). Mean CD4 cell counts increased as current cigarette smoking and lifetime cigarette smoking history increased among participants ($p<0.001$ for both analyses).

Examination of CD5 cells showed a decrease with age ($p=0.008$) and an increase with current cigarette smoking ($p<0.001$) and lifetime cigarette smoking history ($p=0.001$). The enlisted groundcrew had the highest mean CD5 cell count followed by the enlisted flyers and then officers ($p=0.037$).

The mean CD8 cell count increased as current cigarette smoking ($p<0.001$) and lifetime cigarette smoking history ($p=0.044$) increased among participants.

Analysis of CD14 cells revealed non-Black participants had a higher mean CD14 cell count than Black participants ($p=0.005$). The number of CD14 cells increased with age ($p=0.050$), current cigarette smoking ($p<0.001$), lifetime cigarette smoking history ($p<0.001$), and lifetime alcohol history ($p=0.001$). Moderately active participants had the highest mean CD14 cell value followed by sedentary participants and then very active participants ($p=0.025$).

Analysis of CD16+56 cells displayed a significant positive association between CD16+56 cells and age ($p=0.010$) and a significant inverse relationship with current cigarette smoking ($p=0.003$).

CD20 cell counts increased significantly with age ($p<0.001$) and current cigarette smoking ($p<0.001$). Black participants had a significantly higher mean CD20 cell count than non-Black participants ($p=0.047$), and enlisted groundcrew had the highest mean CD20 cell counts followed by enlisted flyers and then officers ($p<0.001$).

CD25 cell counts decreased with age ($p=0.002$) and increased with current cigarette smoking ($p<0.001$), lifetime cigarette smoking history ($p<0.001$), and current alcohol use ($p=0.034$) among participants. Enlisted groundcrew had the highest mean CD25 values followed by enlisted flyers and then officers ($p=0.047$).

Analysis of the CD4-CD8 ratio exhibited a significant negative association with age ($p<0.001$) and a significant positive association with current cigarette smoking ($p=0.002$).

The double labelled cell surface marker analysis of CD3 with CD25 demonstrated a significant inverse association with age ($p=0.005$) and positive associations with current cigarette smoking ($p<0.001$), lifetime cigarette smoking history ($p<0.001$), and current alcohol use ($p=0.035$). Enlisted groundcrew had the highest mean CD3 with CD25 cell count followed by enlisted flyers and then officers ($p=0.035$).

The double labelled cell surface marker CD5 with CD20 contained many measurements of 0 cells/mm^3. Analyses were performed on the nonzero values in their continuous form as well as dichotomized as zero and nonzero. The analysis of nonzero CD5 with CD20 measurements revealed a significant inverse relationship with age ($p<0.001$), lifetime cigarette smoking history ($p=0.009$), current alcohol use ($p<0.001$), and lifetime alcohol history ($p=0.009$). Enlisted groundcrew had the highest mean CD5 with CD20 level followed by the enlisted flyers and then officers ($p=0.001$). The analysis of CD5 with CD20 in its dichotomized form showed that the prevalence of zero values increased significantly with current alcohol use ($p=0.038$).

Similarly, two analyses were performed on the double labelled cell surface marker CD4 with CD8 due to the presence of 0 cells/mm^3 measurements. The analysis performed on the nonzero CD4 with CD8 measurements revealed a significant positive relationship with current cigarette smoking ($p<0.001$). The analysis of CD4 with CD8 when categorized as zero or nonzero revealed a higher percentage of the younger participants with no CD4 with CD8 cells present ($p=0.037$).

Both discrete (zero vs. nonzero) and continuous (nonzero measurements only) analyses were performed on double labelled CD3 with CD16+56 cells. The analysis of nonzero CD3 with CD16+56 cells revealed a significant positive relationship with age ($p<0.001$). The analysis of the nonzero CD3 with CD16+56 cell showed Black participants had a higher mean CD3 with CD16 cell count than non-Black participants ($p<0.001$).

TLC decreased with age ($p=0.005$) and increased with current cigarette smoking ($p<0.001$) and lifetime cigarette smoking history ($p<0.001$). The enlisted groundcrew had the highest mean TLC followed by enlisted flyers and officers ($p=0.002$).

The immunoglobulin IgA increased significantly with age ($p=0.002$) and lifetime alcohol history ($p=0.031$).

Black participants had a significantly higher mean level of the immunoglobulin IgG than non-Black participants ($p<0.001$). IgG decreased with current cigarette smoking ($p<0.001$), lifetime cigarette smoking history ($p<0.001$), current alcohol use ($p=0.016$),

and lifetime alcohol history ($p=0.039$). The enlisted groundcrew had the highest mean IgG level followed by enlisted flyers and officers ($p=0.002$).

The mean levels of the immunoglobulin IgM decreased with age ($p=0.002$) and increased with current alcohol use ($p=0.026$). Mean IgM levels were higher in non-Black participants than in Black participants ($p=0.003$).

Older participants had a significantly higher percentage of abnormal results in the lupus panel antinuclear antibody (ANA) test ($p<0.001$), the mouse stomach kidney (MSK) smooth muscle antibody test ($p=0.008$), and the rheumatoid factor ($p=0.002$) than the younger participants.

The analysis of B cell clones detected by serum protein electrophoresis revealed an increase in positive results with age ($p=0.024$) and lifetime cigarette smoking history ($p=0.012$). Enlisted flyers had the highest percentage of positive results followed by officers and enlisted groundcrew ($p=0.033$). Participants who smoked between 0 and 20 cigarettes per day had the highest percentage of B cell clones detected, followed by those who formerly smoked, those who smoke 20 or more cigarettes per day, and those who have never smoked ($p=0.006$).

The lupus panel summary index was constructed from the eight individual tests and scored as abnormal if any of the eight individual tests were abnormal and normal if all eight tests were normal. Older participants had a higher percentage of an abnormal summary index than the younger participants ($p<0.001$). Officers had the highest percentage of abnormal findings in the summary index followed by enlisted flyers and then enlisted groundcrew ($p=0.009$).

Exposure Analysis

The following section presents the results of the statistical analyses of the dependent variables shown in Table 19-2. Dependent variables are grouped into two sections: one variable obtained during the 1992 physical examination and data derived from the immunology laboratory portion of the 1992 followup examination.

Unadjusted and adjusted analyses of six models are presented for each variable. Model 1 examines the relationship between the dependent variable and group (Ranch Hand or Comparison). Model 2 explores the relationship 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, a 1992 level was used. A statistical adjustment for the percent of body fat at the participant's time of duty in SEA and the change in the percent of body fat from the time of duty in SEA to the date of the blood draw for dioxin is included in this model to account for body-fat-related differences in elimination rate (52). Model 3 dichotomizes the Ranch Hands in Model 2 based on their initial dioxin measures; these two categories of Ranch Hands are referred to as the "low Ranch Hand" category and the "high Ranch Hand" category. These participants are added to Ranch Hands and Comparisons with current serum dioxin levels (1987, if available; 1992, if the 1987 level was not available) at or below 10 ppt to create a total of four categories.

Ranch Hands with current serum dioxin levels at or below 10 ppt are referred to as the "background Ranch Hand" category. The relationship between the dependent variable in each of the three Ranch Hand categories and the dependent variable in the "Comparison" category is examined. A fourth contrast, exploring the relationship of the dependent variable in the low Ranch Hand category and the high Ranch Hand category combined, also is conducted. This combination is referred to in the text and tables as the "low plus high Ranch Hand" category. As in Model 2, a statistical adjustment is made for the percent of body fat at the participant's time of duty in SEA and the change in the percent of body fat from the time of duty in SEA to the date of the blood draw for dioxin.

Models 4, 5, and 6 examine the relationship between the dependent variable and 1987 dioxin levels in all Ranch Hands with a dioxin measurement. If a participant did not have a 1987 dioxin measurement, a 1992 measurement was utilized in determining the current dioxin level. The measure of dioxin in Model 4 is lipid-adjusted, whereas whole-weight dioxin is used in Models 5 and 6. Model 6 differs from Model 5 in that a statistical adjustment for total lipids is included in Model 6. Further details on dioxin and the modeling strategy are found in Chapters 2 and 7 respectively.

Results of investigation for group-by-covariate and dioxin-by-covariate interactions are referenced in the text, and tabular results are presented in Appendix O-2. As described previously, additional analyses were performed when occupation was retained in the final models for Models 2 through 6. Results excluding occupation from these models are tabled in Appendix O-3, and dioxin-by-covariate interactions with occupation excluded from these models are presented in Appendix O-4. Results from analyses excluding occupation are discussed in the text only if a meaningful change occurred (that is, changes between significant results, marginally significant results, and nonsignificant results).

Physical Examination Variable

Composite Skin Test Diagnosis

A composite skin test diagnosis was constructed based on the response to four separate antigens injected intradermally to measure antigen reactivity or sensitivity. If none of the four antigen responses were positive, the composite skin test diagnosis was scored "possibly abnormal." If one or more of the four antigen responses was positive, the composite skin test was considered "normal."

Analysis of the composite skin test did not reveal a significant difference between Ranch Hands and Comparisons in the unadjusted analyses of Model 1 (Table 19-4(a): $p > 0.11$ for all unadjusted analyses). Overall, the adjusted analysis did not display a significant association between Ranch Hands and Comparisons; however, stratifying by occupation revealed a marginally significant difference between Ranch Hand and Comparison officers (Table 19-4(b): $p=0.131$ and $p=0.084$, Adj. RR=1.87 respectively). The covariates age, race, and current cigarette smoking were retained in the final adjusted model.

Model 2 did not display a significant association between initial dioxin and the composite skin test diagnosis (Table 19-4(c,d): $p > 0.16$ for both the unadjusted and adjusted

Table 19-4.
Analysis of Composite Skin Test Diagnosis

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Possibly Abnormal**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***919***	***4.2***	***1.46 (0.92,2.31)***	***0.136***
	Comparison	***1,220***	***3.0***		
Officer	Ranch Hand	354	5.4	1.87 (0.92,3.78)	0.113
	Comparison	475	2.9		
Enlisted Flyer	Ranch Hand	158	3.8	1.22 (0.39,3.87)	0.961
	Comparison	192	3.1		
Enlisted Groundcrew	Ranch Hand	407	3.4	1.20 (0.58,2.48)	0.769
	Comparison	553	2.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.43 (0.90,2.28)***	***0.131***	AGE (p=0.001) RACE (p=0.005) CSMOK (p=0.026)
Officer	1.87 (0.92,3.80)	0.084	
Enlisted Flyer	1.14 (0.36,3.62)	0.828	
Enlisted Groundcrew	1.18 (0.57,2.46)	0.659	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-4. (Continued)
Analysis of Composite Skin Test Diagnosis

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Possibly Abnormal	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	169	5.3	0.77 (0.49,1.22)	0.240
Medium	170	1.8		
High	167	1.8		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
499	0.74 (0.47,1.16)	0.163	RACE (p=0.064) ALC (p=0.024)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-4. (Continued)
Analysis of Composite Skin Test Diagnosis

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Possibly Abnormal	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,019	2.9		
Background RH	358	6.1	1.93 (1.09,3.43)	0.024
Low RH	252	4.0	1.37 (0.65,2.85)	0.407
High RH	254	2.0	0.71 (0.27,1.87)	0.491
Low plus High RH	506	3.0	1.05 (0.55,1.98)	0.886

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,004			DXCAT*ALC (p=0.022) AGE (p=0.024) RACE (p=0.008) CSMOK (p=0.120)
Background RH	356	1.80 (1.01,3.20)**	0.047**	
Low RH	249	1.41 (0.67,2.97)**	0.363**	
High RH	250	0.78 (0.30,2.06)**	0.435**	
Low plus High RH	499	1.11 (0.59,2.12)**	0.744**	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-1 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.
DXCAT = Categorized Dioxin.

Table 19-4. (Continued)
Analysis of Composite Skin Test Diagnosis

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Possibly Abnormal/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	6.0 (283)	5.2 (289)	1.7 (292)	0.72 (0.56,0.93)	0.008
5	6.3 (288)	5.2 (286)	1.4 (290)	0.78 (0.65,0.94)	0.012
6[c]	6.3 (287)	5.2 (286)	1.4 (290)	0.78 (0.63,0.95)	0.014

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	845	0.76 (0.59,0.98)	0.029	AGE (p=0.085) RACE (p=0.048) DRKYR (p=0.147) CSMOK (p=0.119)
5	864	0.82 (0.68,0.99)	0.037	AGE (p=0.044) RACE (p=0.050) CSMOK (p=0.084)
6[d]	863	0.80 (0.64,0.99)**	0.047**	CURR*OCC (p=0.039) AGE (p=0.040) RACE (p=0.030) CSMOK (p=0.114)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-1 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.
CURR = Log_2 (current dioxin + 1).

analyses). Race and current alcohol use were included in the final adjusted model. In Model 3, the unadjusted analysis exhibited a significantly higher percentage of abnormal skin tests in background Ranch Hands (6.1%) than in Comparisons (2.9%) (Table 19-4(e): p=0.024, Est. RR=1.93). Adjusting for covariates in Model 3 revealed a significant categorized dioxin-by-current alcohol use interaction (Table 19-4(f): p=0.022). Stratified results of the interaction between current alcohol use and categorized dioxin are presented in Appendix Table O-2-1. Removal of the interaction revealed a significant difference between background Ranch Hands and Comparisons (Table 19-4(f): p=0.047, Adj. RR=1.80). Age, race, and current cigarette smoking also were in the final adjusted model.

The unadjusted analyses of Models 4 through 6 showed significant inverse associations between the composite skin test diagnosis and current dioxin (Table 19-4(g): p=0.008, Est. RR=0.72; p=0.012, Est. RR=0.78; and p=0.014, Est. RR=0.78 for Models 4, 5, and 6 respectively). The adjusted analysis for composite skin test also revealed significant inverse relationships with current dioxin in Models 4 and 5 (Table 19-4(h): p=0.029, Adj. RR=0.76 and p=0.037, Adj. RR=0.82). The final adjusted model of Model 4 contained the covariates age, race, lifetime alcohol history, and current cigarette smoking. Model 5 contained age, race, and current cigarette smoking in the final adjusted model. Adjusting for covariates in Model 6 revealed a significant current dioxin-by-occupation interaction (Table 19-4(h): p=0.039). In Model 6, the covariates age, race, and current cigarette smoking also were retained in the final adjusted model. Removal of the interaction from the model revealed a significant inverse association between current dioxin and composite skin test diagnosis (Table 19-4(h): p=0.047, Adj. RR=0.80). Further analyses of the current dioxin-by-occupation interaction stratified by occupation were performed. These stratified results are presented in Appendix Table O-2-1. When occupation was removed from the Model 6 final adjusted model, the association between current dioxin and composite skin test diagnosis became marginally significant (Appendix Table O-3-1(a): p=0.062).

Laboratory Examination Variables

CD3 Cells

The unadjusted Model 1 analysis discovered a significant difference in mean CD3 cell count between Ranch Hand and Comparison officers (Table 19-5(a): p=0.039). Ranch Hand officers had a higher mean CD3 cell count (1,474.0 cells/mm^3) than Comparison officers (1,326.5 cells/mm^3). After adjusting for current cigarette smoking, the Model 1 analyses were nonsignificant (Table 19-5(b): p>0.13).

The unadjusted analysis of Models 2 and 3 did not find any significant associations between CD3 cell count and initial dioxin (Table 19-5(c,e): p>0.29). The adjusted Model 2 analysis revealed a significant interaction between initial dioxin and occupation (Table 19-5(d): p=0.032). Stratified analyses of this interaction are presented in Appendix Table O-2-2. Age, current cigarette smoking, and lifetime alcohol use also were included in the final adjusted Model 2 analysis. After removing the interaction with initial dioxin from the adjusted model, the results were nonsignificant (Table 19-5(d): p=0.760). The adjusted Model 3 analysis also detected significant categorized dioxin-by-age and categorized dioxin-by-occupation interactions (Table 19-5(f): p=0.015 and p=0.012). For further investigation

Table 19-5.
Analysis of CD3 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[ab]**	**Difference of Means (95% C.I.)[c]**	**p-Value[d]**
All	***Ranch Hand***	***367***	***1,481.0***	***23.0 --***	***0.584***
	Comparison	***482***	***1,458.0***		
Officer	Ranch Hand	154	1,474.0	147.5 --	0.039
	Comparison	176	1,326.5		
Enlisted Flyer	Ranch Hand	66	1,436.6	-109.3 --	0.450
	Comparison	83	1,545.9		
Enlisted Groundcrew	Ranch Hand	147	1,542.8	57.8 --	0.390
	Comparison	223	1,485.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[ae]**	**Difference of Adj. Means (95% C.I.)[c]**	**p-Value[d]**	**Covariate Remarks[f]**
All	***Ranch Hand***	***367***	***1,483.4***	***24.4 --***	0.544	CSMOK ($p<0.001$)
	Comparison	***481***	***1,459.0***			
Officer	Ranch Hand	154	1,481.5	93.2 --	0.134	
	Comparison	176	1,388.3			
Enlisted Flyer	Ranch Hand	66	1,410.0	-122.3 --	0.201	
	Comparison	83	1,532.3			
Enlisted Groundcrew	Ranch Hand	147	1,523.1	31.6 --	0.619	
	Comparison	222	1,491.5			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-5. (Continued)
Analysis of CD3 Cells (cells/mm^3)

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	64	1,390.4	1,414.3	0.476	0.013 (0.026)	0.627
Medium	67	1,538.7	1,568.9			
High	72	1,534.9	1,506.6			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			**Analysis Results for Log_2 (Initial Dioxin)[d]**			
Initial Dioxin	**n**	**Adj. Mean[ad]**	**R^2**	**Adj. Slope (Std. Error)[c]**	**p-Value**	**Covariate Remarks**
Low	64	1,528.7**	0.558	-0.010 (0.031)**	0.760**	INIT*OCC (p=0.032) AGE (p=0.095) CSMOK (p=0.006) DRKYR (p=0.092)
Medium	65	1,592.0**				
High	71	1,520.2**				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD3 cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-2 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.
INIT = Log_2 (initial dioxin).

Table 19-5. (Continued)
Analysis of CD3 Cells (cells/mm^3)

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	404	1,440.7	1,440.3		
Background RH	141	1,494.0	1,499.7	59.4 --	0.321
Low RH	95	1,384.6	1,387.1	-53.2 --	0.428
High RH	108	1,515.5	1,509.0	68.7 --	0.298
Low plus High RH	203	1,452.8	1,450.7	10.4 --	0.841

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	1,445.2**			DXCAT*AGE (p=0.015) DXCAT*OCC (p=0.012) CSMOK (p<0.001) ALC (p=0.064)
Background RH	140	1,507.9**	62.7 --**	0.301**	
Low RH	95	1,419.6**	-25.6 --**	0.700**	
High RH	106	1,492.2**	47.0 --**	0.472**	
Low plus High RH	201	1,457.4**	12.2 --**	0.809**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-2 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-5. (Continued)
Analysis of CD3 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	1,470.2 (116)	1,515.4 (107)	1,515.4 (121)	0.296	-0.002 (0.017)	0.896
5	1,487.1 (112)	1,395.5 (116)	1,395.5 (116)	0.296	-0.001 (0.015)	0.967
6[e]	1,450.1 (112)	1,504.7 (116)	1,504.7 (116)	0.300	-0.008 (0.016)	0.629

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	1,458.1 (115)	1,516.7 (107)	1,446.2 (119)	0.353	-0.000 (0.016)	0.988	CSMOK (p<0.001) ALC (p=0.079)
5	1,507.5 (111)	1,414.9 (116)	1,506.7 (114)	0.353	0.003 (0.014)	0.855	CSMOK (p<0.001) ALC (p=0.077)
6[e]	1,503.6 (111)	1,399.3 (116)	1,449.7 (114)	0.366	-0.008 (0.015)	0.616	CSMOK (p<0.001) ALC (p=0.060) PHYACT (p=0.145)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD3 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

of these interactions, stratified analyses are presented in Appendix Table O-2-2. The adjusted Model 3 analysis also accounted for current cigarette smoking and current alcohol use. After removing the interactions from the adjusted model, the Model 3 results were nonsignificant (Table 19-5(f): $p > 0.30$).

None of the unadjusted or adjusted analyses of Models 4 through 6 displayed any significant relationships between current dioxin and CD3 cell count (Table 19-5(g,h): $p > 0.61$). Current cigarette smoking and current alcohol use were retained in the final adjusted analyses of Models 4 through 6, and Model 6 also included physical activity index.

CD4 Cells

The unadjusted Model 1 analysis of CD4 cell count exhibited a marginally significant difference between Ranch Hand and Comparison officers (Table 19-6(a): $p = 0.054$). Ranch Hand officers had a higher mean CD4 cell count (964.5 cells/mm^3) than Comparison officers (873.0 cells/mm^3). After adjusting for age and current cigarette smoking, the Model 1 analysis was nonsignificant (Table 19-6(b): $p > 0.20$).

The unadjusted and adjusted Model 2 analysis of CD4 cells as well as the unadjusted Model 3 analysis did not detect any significant associations between dioxin and CD4 cell counts (Table 19-6(c,d,e): $p > 0.24$). The final adjusted Model 2 analysis accounted for current cigarette smoking. The Model 3 adjusted analysis revealed significant interactions between categorized dioxin and age and occupation (Table 19-6(f): $p = 0.041$ and $p = 0.047$). Stratified analyses of these interactions are presented in Appendix Table O-2-3. The adjusted Model 3 analysis also accounted for current cigarette smoking. After removing the interactions with categorized dioxin from the adjusted model, the Model 3 results were nonsignificant (Table 19-6(f): $p > 0.33$ for all contrasts).

The unadjusted analyses of Models 4 through 6 did not reveal any significant relationships between CD4 cells and current dioxin (Table 19-6(g,h): $p > 0.64$). The final models for Models 4 through 6 were adjusted for current cigarette smoking.

CD5 Cells

The unadjusted Model 1 analysis of CD5 cells detected a significant difference between Ranch Hand and Comparison officers (Table 19-7(a): $p = 0.035$). Ranch Hand officers had a higher mean CD5 cell count (1,524.7 cells/mm^3) than Comparison officers (1,366.7 cells/mm^3). The adjusted Model 1 analysis was nonsignificant (Table 19-7(b): $p > 0.13$). Current cigarette smoking, current alcohol use, and physical activity index were included in the final adjusted Model 1 analysis.

The Model 2 and 3 unadjusted analyses of CD5 cells were nonsignificant (Table 19-7(c,e): $p > 0.20$). The adjusted Model 2 analysis detected a significant interaction between initial dioxin and occupation (Table 19-7(d): $p = 0.031$). Stratified analyses were performed for each occupational category and are presented in Appendix Table O-2-4. The final Model 2 analysis also was adjusted for age, current cigarette smoking, and lifetime alcohol history. After removing the interaction from the adjusted model, the Model 2 results

Table 19-6.
Analysis of CD4 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[ab]**	**Difference of Means (95% C.I.)[c]**	**p-Value[d]**
All	***Ranch Hand***	***367***	***953.5***	***15.3 --***	***0.581***
	Comparison	***482***	***938.2***		
Officer	Ranch Hand	154	964.5	91.5 --	0.054
	Comparison	176	873.0		
Enlisted Flyer	Ranch Hand	66	909.3	-83.2 --	0.400
	Comparison	83	992.5		
Enlisted Groundcrew	Ranch Hand	147	998.9	55.0 --	0.217
	Comparison	223	943.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[ac]**	**Difference of Adj. Means (95% C.I.)[c]**	**p-Value[d]**	**Covariate Remarks[f]**
All	***Ranch Hand***	***367***	***956.9***	***19.7 --***	0.454	AGE (p=0.040)
	Comparison	***481***	***937.2***			CSMOK (p<0.001)
Officer	Ranch Hand	154	973.8	53.3 --	0.204	
	Comparison	176	920.5			
Enlisted Flyer	Ranch Hand	66	900.8	-75.5 --	0.227	
	Comparison	83	976.3			
Enlisted Groundcrew	Ranch Hand	147	966.3	28.8 --	0.484	
	Comparison	222	937.5			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-6. (Continued)
Analysis of CD4 Cells (cells/mm^3)

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	64	878.0	894.5	0.465	0.010 (0.027)	0.705
Medium	67	993.5	1,014.8			
High	72	959.4	940.1			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			**Analysis Results for Log_2 (Initial Dioxin)[d]**			
Initial Dioxin	**n**	**Adj. Mean[ad]**	**R^2**	**Adj. Slope (Std. Error)[c]**	**p-Value**	**Covariate Remarks**
Low	64	929.0	0.518	-0.008 (0.026)	0.770	CSMOK ($p<0.001$)
Medium	67	1,008.8				
High	72	919.3				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD4 cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-6. (Continued)
Analysis of CD4 Cells (cells/mm^3)

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	404	922.0	921.8		
Background RH	141	957.4	960.4	38.6 --	0.330
Low RH	95	885.7	889.6	-32.2 --	0.468
High RH	108	977.6	972.5	50.7 --	0.246
Low plus High RH	203	933.4	932.8	11.0 --	0.747

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	403	922.5**			DXCAT*AGE (p=0.041) DXCAT*OCC (p=0.047) CSMOK (p<0.001)
Background RH	141	960.5**	38.0 --**	0.331**	
Low RH	95	916.7**	-5.8 --**	0.893**	
High RH	108	962.1**	39.6 --**	0.348**	
Low plus High RH	203	940.6**	18.1 --**	0.583**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-3 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-6. (Continued)
Analysis of CD4 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	930.0 (116)	944.4 (107)	942.2 (121)	0.269	0.001 (0.017)	0.974
5	970.3 (112)	886.0 (116)	966.7 (116)	0.269	0.003 (0.015)	0.866
6[e]	990.1 (112)	888.2 (116)	951.2 (116)	0.276	-0.007 (0.016)	0.647

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	926.2 (116)	961.9 (107)	936.6 (121)	0.333	0.001 (0.017)	0.972	CSMOK ($p<0.001$)
5	968.4 (112)	897.4 (116)	962.7 (116)	0.333	0.004 (0.014)	0.790	CSMOK ($p<0.001$)
6[e]	987.7 (112)	899.5 (116)	947.7 (116)	0.340	-0.006 (0.016)	0.719	CSMOK ($p<0.001$)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD4 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-7.
Analysis of CD5 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[ab]**	**Difference of Means (95% C.I.)[c]**	**p-Value[d]**
All	***Ranch Hand***	***367***	***1,530.7***	***29.5 --***	***0.497***
	Comparison	***482***	***1,501.2***		
Officer	Ranch Hand	154	1,524.7	158.0 --	0.035
	Comparison	176	1,366.7		
Enlisted Flyer	Ranch Hand	66	1,480.7	105.8 --	0.495
	Comparison	83	1,586.5		
Enlisted Groundcrew	Ranch Hand	147	1,595.9	69.3 --	0.310
	Comparison	223	1,526.6		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[ae]**	**Difference of Adj. Means (95% C.I.)[c]**	**p-Value[d]**	**Covariate Remarks[f]**
All	***Ranch Hand***	***364***	***1,513.7***	***36.6 --***	0.377	AGE (p=0.114) CSMOK (p<0.001) ALC (p=0.132) PHYACT (p=0.103)
	Comparison	***477***	***1,477.1***			
Officer	Ranch Hand	154	1,528.9	97.3 --	0.134	
	Comparison	174	1,431.6			
Enlisted Flyer	Ranch Hand	64	1,437.1	-122.8 --	0.217	
	Comparison	83	1,559.9			
Enlisted Groundcrew	Ranch Hand	146	1,538.1	47.9 --	0.460	
	Comparison	220	1,490.2			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-7. (Continued)
Analysis of CD5 Cells (cells/mm^3)

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	64	1,430.4	1,458.8	0.479	0.016 (0.027)	0.545
Medium	67	1,595.4	1,631.7			
High	72	1,595.5	1,561.8			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	1,582.7**	0.558	-0.008 (0.032)**	0.809**	INIT*OCC (p=0.031)
Medium	65	1,653.8**				AGE (p=0.072)
High	71	1,569.7**				CSMOK (p=0.013)
						DRKYR (p=0.090)

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD5 Cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-4 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-7. (Continued)
Analysis of CD5 Cells (cells/mm^3)

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	404	1,482.2	1,481.8		
Background RH	141	1,533.3	1,539.7	57.9 --	0.348
Low RH	95	1,422.2	1,425.1	-56.7 --	0.412
High RH	108	1,576.1	1,568.7	86.9 --	0.204
Low plus High RH	203	1,502.1	1,499.8	18.0 --	0.737

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	1,486.5**			DXCAT*AGE (p=0.012) DXCAT*OCC (p=0.011) CSMOK (p<0.001) ALC (p=0.038)
Background RH	140	1,548.0**	61.5 --**	0.326**	
Low RH	95	1,464.2**	-22.3 --**	0.745**	
High RH	106	1,552.3**	65.8 --**	0.333**	
Low plus High RH	201	1,510.0**	23.5 --**	0.655**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-4 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-7. (Continued)

Analysis of CD5 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	1,505.4 (116)	1,524.4 (107)	1,510.0 (121)	0.282	0.003 (0.017)	0.865
5	1,553.6 (112)	1,425.3 (116)	1,572.4 (116)	0.282	0.004 (0.015)	0.802
6[d]	1,574.5 (112)	1,427.6 (116)	1,555.7 (116)	0.285	-0.003 (0.016)	0.838

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	1,470.1 (115)	1,532.4 (107)	1,465.8 (119)	0.346	0.002 (0.016)	0.919	CSMOK (p<0.001) ALC (p=0.041) PHYACT (p=0.145)
5	1,520.5 (111)	1,427.1 (116)	1,539.0 (114)	0.346	0.005 (0.014)	0.750	CSMOK (p<0.001) ALC (p=0.039) PHYACT (p=0.149)
6[e]	1,540.8 (111)	1,428.3 (116)	1,517.4 (114)	0.350	-0.003 (0.015)	0.836	CSMOK (p<0.001) ALC (p=0.037) PHYACT (p=0.119)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD5 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

were nonsignificant (Table 19-7(d): p=0.351). The adjusted Model 3 analysis of CD5 cells revealed significant interactions between categorized dioxin and age and occupation (Table 19-7(f): p=0.012 and p=0.011, respectively). For further investigation of these interactions, stratified analyses are presented in Appendix Table O-2-4. The final Model 3 analysis also was adjusted for current cigarette smoking and current alcohol use. The adjusted model after removal of the two interactions with categorized dioxin did not exhibit any significant relationships between categorized dioxin and CD5 cell count (Table 19-7(f): p>0.32).

The unadjusted and adjusted analyses of Models 4 through 6 did not detect any significant relationships between current dioxin and CD5 cells (Table 19-7(g,h): p>0.75). Current cigarette smoking, current alcohol use, and physical activity index were retained in the final adjusted analyses of Models 4 through 6.

CD8 Cells

Both the unadjusted and adjusted Model 1 analyses of CD8 cells revealed a marginally significant difference in mean CD8 cell counts between Ranch and Comparison enlisted flyers (Table 19-8(a,b): p=0.053 unadjusted; p=0.055 adjusted). Ranch Hand enlisted flyers had a lower mean CD8 cell count (603.8 and 597.5 cells/mm^3 unadjusted and adjusted) than Comparison enlisted flyers (700.9 and 691.9 cells/mm^3 unadjusted and adjusted). The adjusted Model 1 analyses accounted for current cigarette smoking.

The unadjusted Model 2 and 3 analyses of CD8 cell counts were nonsignificant (Table 19-9(c,e): p>0.44). The adjusted Model 2 analysis displayed a highly significant interaction between initial dioxin and occupation, and results stratified by occupation are presented in Appendix Table O-2-5. Officers displayed a significant positive association between CD8 cell counts and initial dioxin (Appendix Table O-2-5(a): p=0.007, Adj. Slope=0.493). The adjusted Model 2 analysis also accounted for current cigarette smoking and current alcohol use. The adjusted Model 3 analysis also detected significant categorized dioxin-by-age and categorized dioxin-by-occupation interactions. Stratified analyses of these interactions are presented in Appendix Table O-2-5. The final Model 3 analysis also was adjusted for current cigarette smoking and current alcohol use. After removing the interactions from the adjusted model, the results were nonsignificant (Table 19-8(f): p>0.40).

The unadjusted analyses of Models 4 through 6 did not show any significant relationships between current dioxin and CD8 cell counts (Table 19-8(g): p>0.59). The adjusted Model 4 analysis detected a significant interaction between current dioxin and occupation (Table 19-8(h): p=0.050). For further investigation of this interaction, stratified analyses are presented in Appendix Table O-2-5. The final adjusted Model 4 analysis also was adjusted for current cigarette smoking and current alcohol use. After removal of the interaction with current dioxin, the adjusted Model 4 analysis was nonsignificant (Table 19-8(h): p=0.742). Similarly, the adjusted analyses of Models 5 and 6 did not exhibit any significant associations between current dioxin and CD8 cell counts (Table 19-8(h): p>0.66). Models 5 and 6 were adjusted for current cigarette smoking and current alcohol use.

Table 19-8.
Analysis of CD8 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[a]**	**Difference of Means (95% C.I.)[b]**	**p-Value[c]**
All	***Ranch Hand***	***367***	***628.3***	***-4.7 --***	***0.817***
	Comparison	***482***	***633.0***		
Officer	Ranch Hand	154	617.7	24.4 --	0.470
	Comparison	176	593.3		
Enlisted Flyer	Ranch Hand	66	603.8	-97.1 --	0.053
	Comparison	83	700.9		
Enlisted Groundcrew	Ranch Hand	147	651.1	9.7 --	0.746
	Comparison	223	641.4		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***367***	***628.8***	***-3.8 --***	0.851	CSMOK ($p<0.001$)
	Comparison	***481***	***632.6***			
Officer	Ranch Hand	154	626.2	23.5 --	0.453	
	Comparison	176	602.7			
Enlisted Flyer	Ranch Hand	66	597.5	-94.4 --	0.055	
	Comparison	83	691.9			
Enlisted Groundcrew	Ranch Hand	147	646.0	10.3 --	0.745	
	Comparison	222	635.7			

[a] Transformed from the 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-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-8. (Continued)
Analysis of CD8 Cells (cells/mm^3)

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	64	601.4	601.6	0.001	0.008 (0.028)	0.763
Medium	67	615.6	615.8			
High	72	631.2	630.8			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	****	0.136	****	****	INIT*OCC (p=0.001)
Medium	66	****				CSMOK (p=0.009)
High	71	****				ALC (p=0.016)

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of CD8 Cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, and p-value not presented; refer to Appendix Table O-2-5 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-8. (Continued)
Analysis of CD8 Cells (cells/mm^3)

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	404	629.2	629.0		
Background RH	141	636.7	639.1	10.1 --	0.734
Low RH	95	606.3	603.8	-25.2 --	0.447
High RH	108	625.6	625.6	-3.4 --	0.916
Low plus High RH	203	616.5	615.3	-13.7 --	0.588

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	633.6**			DXCAT*AGE (p=0.020) DXCAT*OCC (p=0.001) CSMOK (p<0.001) ALC (p=0.033)
Background RH	140	645.3**	11.7 --**	0.705**	
Low RH	95	606.3**	-27.3 --**	0.413**	
High RH	106	618.4**	-15.2 --**	0.645**	
Low plus High RH	201	612.7**	-20.9 --**	0.409**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-5 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-8. (Continued)
Analysis of CD8 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[b]	Current Dioxin Category Mean[a]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Slope (Std. Error)[c]	p-Value
4	628.4 (116)	652.2 (107)	598.0 (121)	0.001	-0.009 (0.019)	0.639
5	625.5 (112)	629.7 (116)	619.1 (116)	0.001	-0.009 (0.016)	0.592
6[d]	624.9 (112)	629.6 (116)	619.7 (116)	0.001	-0.009 (0.018)	0.602

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[b]	Current Dioxin Category Adjusted Mean[a]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	620.9** (115)	657.5** (107)	574.7** (119)	0.068	-0.007 (0.022)**	0.742**	CURR*OCC (p=0.050) CSMOK (p<0.001) ALC (p=0.078)
5	619.8 (111)	634.5 (116)	612.9 (114)	0.048	-0.006 (0.016)	0.728	CSMOK (p<0.001) ALC (p=0.142)
6[e]	621.3 (111)	634.6 (116)	611.3 (114)	0.048	-0.008 (0.017)	0.663	CSMOK (p<0.001) ALC (p=0.137)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of CD8 cells versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-5 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

CD14 Cells

The Model 1 unadjusted analyses of CD14 cell counts were nonsignificant (Table 19-9(a): $p>0.14$). The adjusted analyses displayed a significant interaction between group and occupation (Table 19-9(b): $p=0.044$). Analyses stratified by occupational category revealed a significant difference in mean CD8 cell counts between Ranch Hand and Comparison enlisted flyers (Table 19-9(b): $p=0.021$). Ranch Hand enlisted flyers had a lower mean CD14 cell count (449.8 cells.mm^3) than Comparison enlisted flyers (505.9 cells/mm^3).

The unadjusted and adjusted Model 2 analyses of CD14 cell counts did not detect a significant relationship with initial dioxin (Table 19-9(c,d): $p>0.24$). Model 2 was adjusted for current cigarette smoking and lifetime alcohol history. The Model 3 unadjusted analysis of CD14 cell counts detected a significant difference between Comparisons and Ranch Hands in the low initial dioxin category and a marginally significant difference between Comparisons and Ranch Hands in the low plus high category (Table 19-9(e): $p=0.033$ and $p=0.092$ respectively). Comparisons had a higher mean CD14 cell count (523.5 cells/mm^3) than Ranch Hands in the low initial dioxin category (483.7 cells/mm^3) and in the low plus high category (500.1 cells/mm^3). The adjusted Model 3 analysis detected a highly significant interaction between categorized dioxin and age (Table 19-9(f): $p=0.002$). Stratified analyses of this interaction are presented in Appendix Table O-2-6. Older Ranch Hands in the low, high, and low plus high dioxin categories had significantly or marginally significantly lower mean CD14 cell counts than Comparisons (Appendix Table O-2-6(b): $p=0.008$, $p=0.061$, and $p=0.003$ respectively). The adjusted Model 3 analysis also accounted for occupation, race, current cigarette smoking, and physical activity index.

None of the unadjusted and adjusted analyses of Models 4 through 6 revealed any significant associations between CD14 cell counts and current dioxin (Table 19-9(g,h): $p>0.38$). Each of Models 4 through 6 were adjusted for age, occupation, race, and current cigarette smoking.

CD16+56 Cells

The unadjusted analysis of Model 1 revealed a marginally significant difference in mean CD16+56 cell count between enlisted flyer Ranch Hands and Comparisons (Table 19-10(a): $p=0.097$). Ranch Hand enlisted flyers had a lower mean CD16+56 cell count (221.5 cells/mm^3) than Comparison enlisted flyers (278.0 cells/mm^3). However, after adjusting for age and current cigarette smoking, the Model 1 analysis of CD16+56 cell counts was nonsignificant (Table 19-10(b): $p>0.11$).

The unadjusted Model 2 and 3 analyses of CD16+56 cells were nonsignificant (Table 19-10(c,e): $p>0.14$). The adjusted Model 2 analysis detected significant interactions between initial dioxin and occupation and physical activity index (Table 19-10(d): $p=0.003$ and $p=0.039$ respectively). Stratified analyses of these interactions are presented in Appendix Table O-2-7. Current cigarette smoking also was included in the adjusted Model 2 analysis. After removal of the interactions from the final model, the Model 2 analysis was nonsignificant (Table 19-10(d): $p=0.724$). Similar to the Model 2 analysis, the adjusted

Table 19-9.
Analysis of CD14 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[ab]	Difference of Means (95% C.I.)[c]	p-Value[d]
All	***Ranch Hand***	***367***	***520.8***	***-2.5 --***	***0.834***
	Comparison	***482***	***523.3***		
Officer	Ranch Hand	154	524.3	30.3 --	0.146
	Comparison	176	494.0		
Enlisted Flyer	Ranch Hand	66	517.5	-20.5 --	0.615
	Comparison	83	538.0		
Enlisted Groundcrew	Ranch Hand	147	524.8	-10.9 --	0.591
	Comparison	223	535.7		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[ae]	Difference of Adj. Means (95% C.I.)[c]	p-Value[d]	Covariate Remarks[f]
All	***Ranch Hand***	***367***	***484.7****	***-2.8 --****	0.784**	GROUP*OCC (p=0.044) AGE (p<0.001) RACE (p=0.001) CSMOK (p<0.001)
	Comparison	***481***	***487.5****			
Officer	Ranch Hand	154	478.1	16.5 --	0.300	
	Comparison	176	461.6			
Enlisted Flyer	Ranch Hand	66	449.8	-56.1 --	0.021	
	Comparison	83	505.9			
Enlisted Groundcrew	Ranch Hand	147	510.7	1.1 --	0.952	
	Comparison	222	509.6			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-6 for further analysis of this interaction.

Table 19-9. (Continued)
Analysis of CD14 Cells (cells/mm^3)

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	64	482.5	488.4	0.394	0.028 (0.024)	0.249
Medium	67	489.5	496.4			
High	72	536.3	529.6			

d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	515.9	0.471	0.009 (0.024)	0.714	CSMOK ($p<0.001$) DRKYR ($p=0.050$)
Medium	65	501.1				
High	71	525.0				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD14 cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-9. (Continued)
Analysis of CD14 Cells (cells/mm^3)

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	404	525.7	523.5		
Background RH	141	530.6	535.1	11.6 --	0.581
Low RH	95	484.9	483.7	-39.8 --	0.033
High RH	108	518.1	515.0	-8.5 --	0.586
Low plus High RH	203	502.3	500.1	-23.4 --	0.092

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	403	****			DXCAT*AGE (p=0.002)
Background RH	141	****	****	****	OCC (p=0.083)
Low RH	95	****	****	****	RACE (p=0.005)
High RH	108	****	****	****	CSMOK (p<0.001)
Low plus High RH	203	****	****	****	PHYACT (p=0.147)

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

**** Categorized dioxin-by-covariate interaction ($p \leq 0.01$); adjusted mean, difference of adjusted means, and p-value not presented; refer to Appendix Table O-2-6 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-9. (Continued)
Analysis of CD14 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[c]	Current Dioxin Category Mean[ab]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Slope (Std. Error)[d]	p-Value
4	525.8 (116)	490.6 (107)	500.7 (121)	0.241	-0.004 (0.014)	0.767
5	525.3 (112)	477.8 (116)	517.5 (116)	0.240	0.000 (0.012)	0.985
6[e]	537.9 (112)	479.2 (116)	507.8 (116)	0.256	-0.012 (0.013)	0.383

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[c]	Current Dioxin Category Adjusted Mean[af]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	474.1 (116)	443.7 (107)	439.4 (121)	0.345	-0.007 (0.016)	0.650	AGE (p=0.016) OCC (p=0.059) RACE (p=0.005) CSMOK (p<0.001)
5	475.5 (112)	430.2 (116)	464.5 (116)	0.345	0.000 (0.014)	0.992	AGE (p=0.016) OCC (p=0.075) RACE (p=0.006) CSMOK (p<0.001)
6[e]	489.9 (112)	435.1 (116)	460.1 (116)	0.354	-0.011 (0.015)	0.461	AGE (p=0.023) OCC (p=0.073) RACE (p=0.010) CSMOK (p<0.001)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD14 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-10.
Analysis of CD16 + 56 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[ab]	Difference of Means (95% C.I.)[c]	p-Value[d]
All	***Ranch Hand***	***367***	***255.0***	***-11.6 --***	***0.253***
	Comparison	***482***	***266.6***		
Officer	Ranch Hand	154	268.4	16.6 --	0.337
	Comparison	176	251.8		
Enlisted Flyer	Ranch Hand	66	221.5	-56.5 --	0.097
	Comparison	83	278.0		
Enlisted Groundcrew	Ranch Hand	147	258.6	-10.3 --	0.541
	Comparison	223	268.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[ae]	Difference of Adj. Means (95% C.I.)[c]	p-Value[d]	Covariate Remarks[f]
All	***Ranch Hand***	***367***	***254.0***	***-13.8 --***	0.171	AGE (p=0.019)
	Comparison	***481***	***267.8***			CSMOK (p=0.004)
Officer	Ranch Hand	154	256.8	3.3 --	0.832	
	Comparison	176	253.5			
Enlisted Flyer	Ranch Hand	66	235.5	-36.8 --	0.115	
	Comparison	83	272.3			
Enlisted Groundcrew	Ranch Hand	147	260.0	-19.1 --	0.236	
	Comparison	222	279.1			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-10. (Continued)
Analysis of CD16 + 56 Cells (cells/mm^3)

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	64	255.2	257.6	0.408	-0.007 (0.041)	0.870
Medium	67	241.0	243.6			
High	72	253.4	251.2			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	239.5**	0.506	0.015 (0.049)**	0.752**	INIT*OCC (p=0.003) INIT*PHYACT (p=0.039) CSMOK (p=0.053)
Medium	67	238.9**				
High	72	250.1**				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD16 + 56 cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interactions ($p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-7 for further analysis of these interactions.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-10. (Continued)
Analysis of CD16 + 56 Cells (cells/mm^3)

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	404	261.4	261.4		
Background RH	141	254.8	254.8	-6.6 --	0.647
Low RH	95	240.9	241.7	-19.7 --	0.232
High RH	108	244.9	244.4	-17.0 --	0.277
Low plus High RH	203	243.0	243.2	-18.2 --	0.143

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	399	248.0**			DXCAT*OCC (p=0.048) DXCAT*DRKYR (p=0.026) DXCAT*PHYACT (p=0.038) AGE (p<0.001) RACE (p=0.102) CSMOK (p=0.004)
Background RH	139	242.0**	-6.0 --**	0.678**	
Low RH	94	219.3**	-28.7 --**	0.063**	
High RH	106	236.8**	-11.2 --**	0.465**	
Low plus High RH	200	228.4**	-19.6 --**	0.097**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-7 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-10. (Continued)
Analysis of CD16 + 56 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	244.3 (116)	263.8 (107)	235.1 (121)	0.241	-0.007 (0.024)	0.766
5	250.4 (112)	245.1 (116)	246.5 (116)	0.241	-0.009 (0.020)	0.669
6[e]	248.5 (112)	244.9 (116)	248.0 (116)	0.241	-0.006 (0.022)	0.793

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	243.3 (116)	255.9 (107)	241.6 (121)	0.258	0.004 (0.024)	0.869	AGE (p=0.086) CSMOK (p=0.140)
5	249.2 (112)	236.3 (116)	255.5 (116)	0.257	-0.001 (0.021)	0.967	AGE (p=0.094) CSMOK (p=0.138)
6[e]	246.9 (112)	235.9 (116)	257.7 (116)	0.258	0.003 (0.023)	0.882	AGE (p=0.088) CSMOK (p=0.143)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD16 + 56 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Model 3 analysis detected significant interactions between categorized dioxin and three covariates: occupation, lifetime alcohol history, and the physical activity index (Table 19-10(f): $p=0.048$, $p=0.026$, and $p=0.038$ respectively). Stratified analyses of these interactions are presented in Appendix Table O-2-7. Model 3 also was adjusted for age, race, and current cigarette smoking. After removing the interactions from the adjusted model, marginally significant differences in mean CD16+56 cell counts was detected between Comparisons and Ranch Hands in the low and low plus high dioxin categories (Table 19-10(f): $p=0.063$ and $p=0.097$). Comparisons had a higher mean CD16+56 cell count (248.0 cells/mm^3) than Ranch Hands (low: 219.3 cells/mm^3; low plus high: 228.4 cells/mm^3). When occupation was removed from the Model 3 final adjusted model, the low plus high Ranch Hand versus Comparison contrast became nonsignificant (Appendix Table O-3-7(b): $p=0.115$).

None of the unadjusted or adjusted analyses of Models 4 through 6 revealed a significant relationship between current dioxin and CD16+56 cell counts (Table 19-10(g,h): $p>0.66$). Each of Models 4 through 6 were adjusted for age and current cigarette smoking.

CD20 Cells

The unadjusted Model 1 analysis of CD20 cell counts did not display a significant difference between Ranch Hands and Comparisons (Table 19-11(a): $p>0.15$). The adjusted Model 1 analysis detected a significant interaction between group and lifetime alcohol history (Table 19-11(b): $p=0.024$). Stratified analyses of this interaction are presented in Appendix Table O-2-8. The adjusted Model 1 analysis also accounted for age, occupation, current cigarette smoking, and current alcohol use. After removing the interaction from the model, the Model 1 analysis detected a marginally significant overall difference in mean CD20 cell counts between Ranch Hands and Comparisons (Table 19-11(b): $p=0.083$). Ranch Hands had a higher mean CD20 cell count (232.9 cells/mm^3) than Comparisons (218.3 cells/mm^3).

The unadjusted Model 2 analysis revealed a marginally significant positive association between initial dioxin and CD20 cell counts (Table 19-11(c): $p=0.079$). Mean CD20 cell counts for Ranch Hands in the low, medium, and high initial dioxin categories were 199.1, 233.4, and 241.0 cells/mm^3. The adjusted Model 2 analysis detected a significant interaction between initial dioxin and age (Table 19-11(d): $p=0.049$). Stratified analyses of this interaction are presented in Appendix Table O-2-8. Model 2 also was adjusted for current cigarette smoking, lifetime alcohol history, and current alcohol use. After removal of the interaction with initial dioxin, the adjusted Model 2 analysis was nonsignificant (Table 19-11(d): $p=0.783$). Similarly, the unadjusted Model 3 analysis did not reveal any significant associations between categorized dioxin and CD20 cell counts (Table 19-11(e): $p>0.10$). However, the adjusted Model 3 analysis detected a significant difference in mean CD20 cell counts between Comparisons and Ranch Hands in the background category (Table 19-11(f): $p=0.013$). Ranch Hands had a higher mean CD20 cell count (245.1 cells/mm^3) than Comparisons (214.0 cells/mm^3). Age, occupation, current cigarette smoking, and current alcohol use were included in the Model 3 adjusted analysis.

None of the unadjusted or adjusted analyses of Models 4 through 6 revealed a significant relationship between current dioxin and CD20 cell counts (Table 19-11(g,h):

Table 19-11.
Analysis of CD20 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[a]**	**Difference of Means (95% C.I.)[b]**	**p-Value[c]**
All	***Ranch Hand***	***367***	***228.6***	***11.3 --***	***0.194***
	Comparison	***482***	***217.2***		
Officer	Ranch Hand	154	206.6	16.8 --	0.159
	Comparison	176	189.8		
Enlisted Flyer	Ranch Hand	66	228.8	-7.1 --	0.771
	Comparison	83	235.9		
Enlisted Groundcrew	Ranch Hand	147	253.9	19.6 --	0.154
	Comparison	223	234.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***361***	***232.9*****	***14.6 --*****	0.083**	GROUP*DRKYR (p=0.024)
	Comparison	***475***	***218.3*****			AGE (p<0.001)
Officer	Ranch Hand	153	222.6**	19.2 --**	0.129**	OCC (p=0.117)
	Comparison	173	203.4**			CSMOK (p<0.001)
Enlisted Flyer	Ranch Hand	63	234.6**	-2.3 --**	0.914**	ALC (p=0.030)
	Comparison	83	236.9**			
Enlisted Groundcrew	Ranch Hand	145	235.9**	16.3 --**	0.211**	
	Comparison	219	219.6**			

[a] Transformed from the natural logarithm (x + 1) 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 (x + 1) scale.

[c] P-values based on difference of means on natural logarithm (x + 1) scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-8 for further analysis of this interaction.

Table 19-11. (Continued)
Analysis of CD20 Cells (cells/mm^3)

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	64	196.4	199.1	0.036	0.058 (0.033)	0.079
Medium	67	232.1	233.4			
High	72	245.1	241.0			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	225.3**	0.204	-0.009 (0.033)**	0.783**	INIT*AGE (p=0.049)
Medium	65	226.6**				CSMOK (p<0.001)
High	71	215.9**				DRKYR (p=0.058)
						ALC (p=0.010)

[a] Transformed from natural logarithm (x + 1) scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm (x + 1) of CD20 cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-8 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-11. (Continued)
Analysis of CD20 Cells (cells/mm^3)

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	404	213.6	213.5		
Background RH	141	227.2	228.9	15.4 --	0.203
Low RH	95	209.9	210.8	-2.7 --	0.836
High RH	108	238.2	235.4	21.9 --	0.105
Low plus High RH	203	224.5	223.5	10.0 --	0.336

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	214.0			AGE ($p<0.001$) OCC ($p=0.070$) CSMOK ($p<0.001$) ALC ($p=0.010$)
Background RH	140	245.1	31.1 --	0.013	
Low RH	95	223.9	9.9 --	0.452	
High RH	106	220.2	6.2 --	0.628	
Low plus High RH	201	222.0	8.0 --	0.424	

[a] Transformed from natural logarithm (x + 1) scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Difference of adjusted means after transformation to original scale; confidence interval on difference of adjusted means not presented because analysis was performed on natural logarithm (x + 1) scale.

[d] P-value is based on difference of means on natural logarithm (x + 1) scale.

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-11. (Continued)
Analysis of CD20 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[b]	Current Dioxin Category Mean[a]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Slope (Std. Error)[c]	p-Value
4	222.9 (116)	215.0 (107)	238.2 (121)	0.003	0.022 (0.020)	0.280
5	225.1 (112)	212.1 (116)	240.6 (116)	0.004	0.021 (0.018)	0.250
6[d]	227.8 (112)	212.3 (116)	237.5 (116)	0.006	0.014 (0.019)	0.473

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[b]	Current Dioxin Category Adjusted Mean[a]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	259.8 (115)	252.8 (107)	259.4 (119)	0.136	0.008 (0.020)	0.696	AGE (p=0.001) RACE (p=0.018) CSMOK (p<0.001) PACKYR (p=0.064) ALC (p=0.007)
5	263.3 (111)	247.2 (116)	266.2 (114)	0.137	0.012 (0.017)	0.480	AGE (p=0.002) RACE (p=0.018) CSMOK (p<0.001) PACKYR (p=0.065) ALC (p=0.007)
6[e]	270.6 (111)	250.0 (116)	262.7 (114)	0.142	0.002 (0.019)	0.927	AGE (p=0.001) RACE (p=0.012) CSMOK (p<0.001) PACKYR (p=0.094) ALC (p=0.005)

[a] Transformed from natural logarithm (x + 1) scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm (x + 1) of CD20 cells versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

$p>0.25$). Each of Models 4 through 6 were adjusted for age, race, current cigarette smoking, lifetime smoking history, and current alcohol use.

CD25 Cells

The unadjusted Model 1 analysis of CD25 cell counts were nonsignificant (Table 19-12(a): $p>0.16$). The adjusted Model 1 analysis detected a significant interaction between group and occupation (Table 19-12(b): $p=0.022$). Analyses stratified by occupation detected a significant difference in mean CD25 cell counts between enlisted flyer Ranch Hands and Comparisons (Table 19-12(b): $p=0.015$). Ranch Hand enlisted flyers had a lower mean CD25 cell count (241.5 cells/mm^3) than Comparison enlisted flyers (291.4 cells/mm^3). Model 3 was also adjusted for race, current cigarette smoking, lifetime smoking history, and current alcohol use. After removing the interaction from the adjusted model, no significant overall difference was revealed between all Ranch Hands and Comparisons (Table 19-12(a): $p=0.936$).

The unadjusted and adjusted Model 2 analyses as well as the unadjusted Model 3 analysis were nonsignificant (Table 19-12(c,d,e): $p>0.54$). The adjusted Model 2 analysis accounted for race, current cigarette smoking, and the physical activity index. The adjusted Model 3 analysis detected a significant interactions between categorized dioxin and age, occupation, lifetime smoking history, and lifetime alcohol history (Table 19-12(f): $p=0.022$, $p=0.013$, $p=0.044$, and $p=0.016$ respectively). For further investigation of these interactions, the results of stratified analyses are presented in Appendix Table O-2-9. Race and current cigarette smoking also were accounted for in the adjusted Model 3 analysis. After removing the interactions from the model, no significant association was detected between categorized dioxin and CD25 cell counts (Table 19-12(f): $p>0.54$).

The unadjusted analysis of Models 4 through 6 did not show any significant relationships between current dioxin and CD25 cell counts (Table 19-12(g): $p>0.48$). Similarly, after adjusting for race, current cigarette smoking, lifetime smoking history, and, in Model 4, the physical activity index, the results of Models 4 and 5 remained nonsignificant (Table 19-12(h): $p>0.76$). The adjusted Model 6 analysis of CD5 cell counts revealed a significant interaction between current dioxin and lifetime smoking history (Table 19-12(h): $p=0.034$). Stratified analyses of this interaction are presented in Appendix Table O-2-9. Model 6 also was adjusted for race, current cigarette smoking, and the physical activity index. After removing the interaction from the adjusted model, the Model 6 analysis of CD25 cell counts was nonsignificant (Table 19-12(h): $p=0.449$).

CD4-CD8 Ratio

The Model 1 unadjusted analyses of the CD4-CD8 ratio did not exhibit any significant differences between Ranch Hands and Comparisons (Table 19-13(a): $p>0.29$). The adjusted Model 1 analysis revealed a significant interaction between group and the physical activity index (Table 19-13(b): $p=0.027$). For further investigation of this interaction, stratified analyses are presented in Appendix Table O-2-10. Age, occupation, current cigarette smoking, lifetime smoking history, and lifetime alcohol history also were significant in the

Table 19-12.
Analysis of CD25 Cells (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[ab]	Difference of Means (95% C.I.)[c]	p-Value[d]
All	***Ranch Hand***	***367***	***256.9***	***0.5 --***	***0.953***
	Comparison	***482***	***256.4***		
Officer	Ranch Hand	154	250.9	18.7 --	0.213
	Comparison	176	232.2		
Enlisted Flyer	Ranch Hand	66	227.6	-33.7 --	0.244
	Comparison	83	261.3		
Enlisted Groundcrew	Ranch Hand	147	280.6	21.7 --	0.163
	Comparison	223	258.9		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[ae]	Difference of Adj. Means (95% C.I.)[c]	p-Value[d]	Covariate Remarks[f]
All	***Ranch Hand***	***367***	***276.3*****	***0.8 --*****	0.936**	GROUP*OCC (p=0.022) RACE (p=0.016) CSMOK (p<0.001) ALC (p=0.132) PACKYR (p=0.003)
	Comparison	***481***	***275.5*****			
Officer	Ranch Hand	154	277.6	7.3 --	0.605	
	Comparison	176	270.3			
Enlisted Flyer	Ranch Hand	66	241.5	-49.9 --	0.015	
	Comparison	83	291.4			
Enlisted Groundcrew	Ranch Hand	147	295.4	17.3 --	0.228	
	Comparison	222	278.1			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction.

Table 19-12. (Continued)
Analysis of CD25 Cells (cells/mm^3)

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	64	231.1	233.7	0.511	0.021 (0.035)	0.540
Medium	67	256.4	259.6			
High	72	261.7	258.7			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	279.5	0.596	-0.012 (0.033)	0.729	RACE (p=0.046) CSMOK (p=0.001) PHYACT (p=0.048)
Medium	67	279.1				
High	72	276.1				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD25 cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-12. (Continued)
Analysis of CD25 Cells (cells/mm^3)

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	404	248.9	248.8		
Background RH	141	252.6	254.0	5.2 --	0.680
Low RH	95	243.5	244.2	-4.6 --	0.753
High RH	108	256.8	255.2	6.4 --	0.647
Low plus High RH	203	250.5	250.0	1.2 --	0.913

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	399	268.2**			DXCAT*AGE (p=0.022) DXCAT*OCC (p=0.013) DXCAT*PACKYR (p=0.044) DXCAT*DRKYR (p=0.016) RACE (p=0.085) CSMOK (p<0.001)
Background RH	139	276.4**	8.2 --**	0.540**	
Low RH	94	266.9**	-1.3 --**	0.933**	
High RH	106	270.1**	1.9 --**	0.895**	
Low plus High RH	200	268.6**	0.4 --**	0.970**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-9 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-12. (Continued)
Analysis of CD25 Cells (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[c]	Current Dioxin Category Mean[ab]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Slope (Std. Error)[d]	p-Value
4	239.1 (116)	258.8 (107)	245.3 (121)	0.363	-0.004 (0.021)	0.848
5	248.2 (112)	242.1 (116)	252.7 (116)	0.363	-0.001 (0.019)	0.960
6[e]	254.2 (112)	242.8 (116)	248.0 (116)	0.370	-0.014 (0.020)	0.482

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[c]	Current Dioxin Category Adjusted Mean[af]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	257.5 (116)	278.8 (107)	258.7 (121)	0.457	-0.006 (0.020)	0.762	RACE (p=0.075) CSMOK (p<0.001) PACKYR (p=0.018) PHYACT (p=0.146)
5	282.2 (112)	268.7 (116)	284.6 (116)	0.448	0.002 (0.017)	0.915	RACE (p=0.047) CSMOK (p<0.001) PACKYR (p=0.023)
6[e]	281.0** (112)	264.4** (116)	268.5** (116)	0.472	-0.014 (0.019)**	0.449**	CURR*PACKYR (p=0.034) RACE (p=0.044) CSMOK (p<0.001) PACKYR (p=0.007) PHYACT (p=0.078)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD25 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-9 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-13.
Analysis of CD4-CD8 Ratio

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***367***	***1.534***	***0.047 --***	***0.295***
	Comparison	***482***	***1.487***		
Officer	Ranch Hand	154	1.538	0.037 --	0.631
	Comparison	176	1.501		
Enlisted Flyer	Ranch Hand	66	1.517	0.085 --	0.367
	Comparison	83	1.432		
Enlisted Groundcrew	Ranch Hand	147	1.536	0.039 --	0.549
	Comparison	223	1.497		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]	Covariate Remarks[d]
All	***Ranch Hand***	***361***	***1.532*****	***0.062 --*****	0.154**	GROUP*PHYACT (p=0.027) AGE (p<0.001) OCC (p=0.044) CSMOK (p=0.077) PACKYR (p=0.119) DRKYR (p=0.132)
	Comparison	***475***	***1.470*****			
Officer	Ranch Hand	153	1.605**	0.060 --**	0.417**	
	Comparison	173	1.545**			
Enlisted Flyer	Ranch Hand	63	1.549**	0.136 --**	0.186**	
	Comparison	83	1.413**			
Enlisted Groundcrew	Ranch Hand	145	1.469**	0.035 --**	0.584**	
	Comparison	219	1.434**			

[a] Transformed from the 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-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-10 for further analysis of this interaction.

Table 19-13. (Continued)
Analysis of CD4-CD8 Ratio

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	64	1.506	1.516	0.008	0.004 (0.025)	0.881
Medium	67	1.572	1.577			
High	72	1.569	1.556			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	1.594	0.072	-0.017 (0.026)	0.526	AGE (p=0.071) CSMOK (p=0.043) ALC (p=0.031)
Medium	66	1.583				
High	71	1.510				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of CD4-CD8 ratio versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-13. (Continued)
Analysis of CD4-CD8 Ratio

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	404	1.488	1.488		
Background RH	141	1.500	1.504	0.016 --	0.799
Low RH	95	1.532	1.541	0.053 --	0.470
High RH	108	1.566	1.553	0.065 --	0.357
Low plus High RH	203	1.550	1.548	0.060 --	0.286

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	399	1.479			AGE (p=0.002) OCC (p=0.124) CSMOK (p=0.002) DRKYR (p=0.050)
Background RH	139	1.499	0.020 --	0.756	
Low RH	94	1.576	0.097 --	0.185	
High RH	106	1.566	0.087 --	0.222	
Low plus High RH	200	1.571	0.092 --	0.097	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-13. (Continued)
Analysis of CD4-CD8 Ratio

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[b]	Current Dioxin Category Mean[a]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Slope (Std. Error)[c]	p-Value
4	1.495 (116)	1.485 (107)	1.604 (121)	0.001	0.011 (0.016)	0.510
5	1.531 (112)	1.466 (116)	1.593 (116)	0.003	0.014 (0.014)	0.338
6[d]	1.559 (112)	1.469 (116)	1.564 (116)	0.013	0.003 (0.015)	0.833

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[b]	Current Dioxin Category Adjusted Mean[a]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	1.510 (115)	1.510 (107)	1.588 (119)	0.022	0.003 (0.017)	0.868	AGE (p=0.031) ALC (p=0.095)
5	1.547 (111)	1.490 (116)	1.575 (114)	0.022	0.006 (0.015)	0.657	AGE (p=0.036) ALC (p=0.100)
6[e]	1.572 (111)	1.494 (116)	1.547 (114)	0.030	-0.003 (0.016)	0.833	AGE (p=0.027) ALC (p=0.126)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of CD4-CD8 ratio versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

adjusted Model 1 analysis. The results of the Model 1 analysis after removal of the interaction with group were nonsignificant (Table 19-13(b): $p>0.15$).

The unadjusted and adjusted Model 2 analyses as well as the unadjusted Model 3 analyses of the CD4-CD8 ratio did not exhibit any significant associations between the CD4-CD8 ratio and dioxin (Table 19-13(c-e): $p>0.28$). The adjusted Model 2 analysis accounted for age, current cigarette smoking, and current alcohol use. The Model 3 adjusted analysis of the CD4-CD8 ratio detected a marginally significant difference between Comparisons and Ranch Hands in the low plus high initial dioxin category (Table 19-13(f): $p=0.097$). Ranch Hands had a higher mean CD4-CD8 ratio (1.571) than Comparisons (1.479). Model 3 was adjusted for age, occupation, current cigarette smoking, and lifetime alcohol history. After occupation was removed from the Model 3 final adjusted model, the low plus high Ranch Hand versus Comparison contrast was nonsignificant (Appendix Table O-3-10(a): $p=0.161$).

None of the unadjusted or adjusted analyses of Models 4 through 6 revealed a significant relationship between current dioxin and the CD4-CD8 ratio (Table 19-13(g,h): $p>0.33$). Each of Models 4 through 6 were adjusted for age and current alcohol use.

Double Labelled Cells: CD3 with CD25

The unadjusted Model 1 analysis of CD3 with CD25 revealed no significant differences between Ranch Hands and Comparisons (Table 19-14(a): $p>0.10$ for all occupational categories). In the adjusted analysis, the group-by-occupation interaction was significant (Table 19-14(b): $p=0.029$). The difference in CD3 with CD25 means between Ranch Hands and Comparisons was significant for enlisted flyers ($p=0.022$) but not for officers and enlisted flyers ($p=0.783$ and $p=0.185$ respectively). Among the enlisted flyers, the adjusted CD3 with CD25 means were 190.6 cells/mm^3 for Ranch Hands and 229.4 cells/mm^3 for Comparisons. After removing the group-by-occupation interaction, there was no significant difference between all Ranch Hands and Comparisons ($p=0.949$). Significant covariates retained in the adjusted model were race, current cigarette smoking, and lifetime cigarette smoking history.

In Model 2, the association between initial dioxin and CD3 with CD25 was not significant for the unadjusted and adjusted analyses (Table 19-14(c,d): $p=0.891$ and $p=0.422$). Covariates retained in the final adjusted model were race, current cigarette smoking, and the physical activity index.

No significant results were found in the unadjusted Model 3 analysis of CD3 with CD25 (Table 19-14(e): $p>0.61$ for all contrasts). The adjusted model contained significant interactions of categorized dioxin with occupation, lifetime cigarette smoking history, and lifetime alcohol history (Table 19-14(f): $p=0.008$, $p=0.023$, and $p=0.004$). Stratified results, investigating these interactions, are presented in Appendix Table O-2-11. After removing the interactions from the final model, no significant results were found ($p>0.45$ for all contrasts). Race and current cigarette smoking also were significant covariates in the adjusted model.

Table 19-14.
Analysis of Double Labelled Cells: CD3 with CD25 (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[ab]	Difference of Means (95% C.I.)[c]	p-Value[d]
All	***Ranch Hand***	***367***	***202.6***	***0.3 --***	***0.966***
	Comparison	***482***	***202.3***		
Officer	Ranch Hand	154	195.9	14.1 --	0.250
	Comparison	176	181.9		
Enlisted Flyer	Ranch Hand	66	175.2	-31.8 --	0.151
	Comparison	83	207.0		
Enlisted Groundcrew	Ranch Hand	147	226.0	21.8 --	0.102
	Comparison	223	204.2		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[ae]	Difference of Adj. Means (95% C.I.)[c]	p-Value[d]	Covariate Remarks[f]
All	***Ranch Hand***	***367***	***218.8****	***0.5 --****	0.949**	GROUP*OCC (p=0.029) RACE (p=0.014) CSMOK (p<0.001) PACKYR (p=0.001)
	Comparison	***481***	***218.3****			
Officer	Ranch Hand	154	217.8	3.1 --	0.783	
	Comparison	176	214.6			
Enlisted Flyer	Ranch Hand	66	190.6	-38.8 --	0.022	
	Comparison	83	229.4			
Enlisted Groundcrew	Ranch Hand	147	237.1	16.0 --	0.185	
	Comparison	222	221.1			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-11 for further analysis of this interaction.

Table 19-14. (Continued)
Analysis of Double Labelled Cells: CD3 with CD25 (cells/mm^3)

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	64	186.0	188.9	0.511	0.005 (0.038)	0.891
Medium	67	206.0	209.7			
High	72	201.3	198.1			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	225.9	0.587	-0.029 (0.036)	0.422	RACE (p=0.078) CSMOK (p=0.001) PHYACT (p=0.087)
Medium	67	223.9				
High	72	210.2				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD3 with CD25 cells versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-14. (Continued)
Analysis of Double Labelled Cells: CD3 with CD25 (cells/mm^3)

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	404	196.1	196.0		
Background RH	141	199.7	201.1	5.1 --	0.635
Low RH	95	193.2	193.7	-2.3 --	0.850
High RH	108	203.5	202.0	6.0 --	0.614
Low plus High RH	203	198.6	198.1	2.1 --	0.827

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	399	212.7**			DXCAT*OCC (p=0.008) DXCAT*PACKYR (p=0.023) DXCAT*DRKYR (p=0.004) RACE (p=0.043) CSMOK (p<0.001)
Background RH	139	221.1**	8.4 --**	0.456**	
Low RH	94	211.6**	-1.1 --**	0.931**	
High RH	106	215.3**	2.6 --**	0.827**	
Low plus High RH	200	213.5**	0.8 --**	0.926**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-11 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-14. (Continued)
Analysis of Double Labelled Cells: CD3 with CD25 (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[c]	Current Dioxin Category Mean[ab]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Slope (Std. Error)[d]	p-Value
4	186.0 (116)	207.7 (107)	193.1 (121)	0.365	-0.007 (0.023)	0.750
5	194.6 (112)	192.3 (116)	199.1 (116)	0.365	-0.004 (0.020)	0.859
6[e]	199.4 (112)	192.9 (116)	195.3 (116)	0.372	-0.018 (0.022)	0.414

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[c]	Current Dioxin Category Adjusted Mean[af]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	206.6 (116)	229.7 (107)	213.3 (121)	0.449	-0.005 (0.022)	0.826	RACE (p=0.066) CSMOK (p<0.001) PACKYR (p=0.013)
5	221.1 (112)	212.6 (116)	224.2 (116)	0.449	-0.000 (0.019)	0.986	RACE (p=0.068) CSMOK (p<0.001) PACKYR (p=0.012)
6[e]	220.4 (112)	209.5 (116)	211.4 (116)	0.471	-0.017 (0.020)**	0.397**	CURR*PACKYR (p=0.042) RACE (p=0.061) CSMOK (p<0.001) PHYACT (p=0.098)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD3 with CD25 cells versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-11 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

No significant associations between current dioxin and CD3 with CD25 were found in the unadjusted and adjusted analyses of Models 4, 5, and 6 (Table 19-14(g,h): $p > 0.39$ for all analyses). The adjusted Model 6 analysis revealed a significant current dioxin-by-lifetime cigarette smoking history interaction ($p=0.042$). Stratified results are presented in Appendix Table O-2-11. Race, current cigarette smoking, and lifetime cigarette smoking were included in the adjusted analyses for Models 4 and 5. In Model 6, race, current cigarette smoking, and the physical activity index were retained in the final model.

Double Labelled Cells: CD5 with CD20 Cells

Because 4.7 percent (40/849) of the CD5 with CD20 measurements were 0 cells/mm^3, the analysis was conducted in two parts. First, the proportion of CD5 with CD20 cell counts equal to 0 was examined for an association with exposure. Second, only nonzero measurements were explored for an association with exposure.

For Model 1 analysis, no associations between the proportion of CD5 with CD20 cell counts equal to zero and group were observed (Table 19-15(a1,b1): $p \geq 0.31$).

Based on the nonzero CD5 with CD20 cells counts, the Model 1 unadjusted analysis detected a significant difference between Ranch Hand and Comparison enlisted groundcrew (Table 19-15(a2): $p=0.046$). Ranch Hand enlisted groundcrew had a significantly higher mean CD5 with CD20 cell count (65.2 cells/mm^3) than Comparison enlisted groundcrew (54.7 cells/mm^3). However, after adjusting for age and current alcohol use, the Model 1 results were nonsignificant (Table 19-15(b2): $p > 0.16$ for all contrasts).

The unadjusted Model 2 analysis of the dichotomized CD5 with CD20 cell counts was nonsignificant (Table 19-15(c2): $p=0.248$). However, after adjusting for current cigarette smoking, lifetime cigarette smoking history, and lifetime alcohol history, the Model 2 analysis showed a marginally significant negative association between the proportion of zero CD5 with CD20 cell counts and initial dioxin (Table 19-15(d1): $p=0.068$, Adj. RR=0.57).

The Model 2 unadjusted and adjusted analyses did not reveal a significant association between nonzero CD5 with CD20 measurements and initial dioxin (Table 19-15(c2,d2): $p > 0.13$). The Model 2 analysis was adjusted for age, current cigarette smoking, lifetime cigarette smoking history, current alcohol use, and the physical activity index.

No significant associations were found between the proportion of zero CD5 with CD20 cell counts and categorized dioxin or current dioxin (Table 19-15(e1-h1): $p > 0.12$ for all unadjusted and adjusted contrasts).

The Model 3 unadjusted analysis detected a marginally significant difference in mean CD5 with CD20 cell counts between Ranch Hands in the high initial dioxin category and Comparisons (Table 19-15(e2): $p=0.084$, 59.2 cells/mm^3 versus 50.6 cells/mm^3 respectively). After adjusting for age and current alcohol use, the Model 3 results were nonsignificant (Table 19-15(f2): $p > 0.11$).

Table 19-15.
Analysis of Double Labelled Cells: CD5 with CD20
(Zero vs. Nonzero)

a1) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Zero**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***367***	***5.2***	***1.20 (0.64,2.26)***	***0.693***
	Comparison	***482***	***4.4***		
Officer	Ranch Hand	154	6.5	1.04 (0.43,2.52)	0.999
	Comparison	176	6.2		
Enlisted Flyer	Ranch Hand	66	3.0	0.62 (0.11,3.48)	0.895
	Comparison	83	4.8		
Enlisted Groundcrew	Ranch Hand	147	4.8	1.81 (0.60,5.49)	0.441
	Comparison	223	2.7		

b1) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.18 (0.62,2.24)***	***0.625***	AGE ($p<0.001$)
Officer	1.06 (0.43,2.61)	0.906	PACKYR ($p=0.033$)
Enlisted Flyer	0.64 (0.11,3.64)	0.613	CSMOK ($p=0.080$)
Enlisted Groundcrew	1.80 (0.58,5.60)	0.310	ALC ($p=0.138$)

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20 (cells/mm^3)
(Nonzero Measurements)

a2) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***348***	***54.2***	***2.4 --***	***0.424***
	Comparison	***461***	***51.8***		
Officer	Ranch Hand	144	47.9	3.6 --	0.430
	Comparison	165	44.3		
Enlisted Flyer	Ranch Hand	64	48.0	-2.6 --	0.802
	Comparison	79	50.6		
Enlisted Groundcrew	Ranch Hand	140	65.2	10.5 --	0.046
	Comparison	217	54.7		

b2) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]	Covariate Remarks[d]
All	***Ranch Hand***	***345***	***55.1***	***4.2 --***	0.162	AGE ($p<0.001$)
	Comparison	***456***	***50.9***			ALC ($p=0.006$)
Officer	Ranch Hand	144	52.8	4.4 --	0.342	
	Comparison	163	48.4			
Enlisted Flyer	Ranch Hand	62	53.0	-0.6 --	0.939	
	Comparison	79	53.6			
Enlisted Groundcrew	Ranch Hand	139	58.6	6.6 --	0.174	
	Comparison	214	52.1			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Note: Analysis based on measurements above 0 cells/mm^3 only.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20
(Zero vs. Nonzero)

c1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Zero	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	64	7.8	0.72 (0.41,1.29)	0.248
Medium	67	6.0		
High	72	4.2		

d1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
	Analysis Results for Log_2 (Initial Dioxin)[c]		
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
200	0.57 (0.30,1.09)	0.068	PACKYR ($p<0.001$) DRKYR ($p=0.087$) CSMOK ($p=0.008$)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20 (cells/mm^3)
(Nonzero Measurements)

c2) 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	59	48.1	49.6	0.457	0.089 (0.058)	0.131
Medium	63	59.4	61.4			
High	69	64.1	62.0			

d2) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	59	62.4	0.533	-0.040 (0.066)	0.542	AGE (p=0.066)
Medium	62	57.9				CSMOK (p=0.030) PACKYR (p=0.117)
High	68	52.0				ALC (p=0.038) PHYACT (p=0.134)

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD5 with CD20 versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20
(Zero vs. Nonzero)

e1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Zero	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	404	4.5		
Background RH	141	2.8	0.52 (0.17,1.58)	0.246
Low RH	95	8.4	1.96 (0.81,4.72)	0.134
High RH	108	3.7	0.96 (0.31,2.93)	0.939
Low plus High RH	203	5.9	1.45 (0.68,3.12)	0.338

f1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	400			AGE (p<0.001) PACKYR (p=0.010) CSMOK (p=0.072) ALC (p=0.078)
Background RH	140	0.49 (0.16,1.53)	0.219	
Low RH	95	2.05 (0.82,5.13)	0.126	
High RH	106	1.29 (0.41,4.07)	0.666	
Low plus High RH	201	1.70 (0.77,3.77)	0.187	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20 (cells/mm^3)
(Nonzero Measurements)

e2) 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	386	49.7	50.6		
Background RH	137	48.5	49.8	-0.8 --	0.842
Low RH	87	50.3	51.8	1.2 --	0.808
High RH	104	58.8	59.2	8.6 --	0.084
Low plus High RH	191	54.8	53.7	5.1 --	0.189

f2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	382	49.7			AGE ($p<0.001$) ALC ($p=0.007$)
Background RH	136	51.4	1.7 --	0.681	
Low RH	87	56.2	6.5 --	0.207	
High RH	102	55.2	5.5 --	0.242	
Low plus High RH	189	55.7	6.0 --	0.115	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
RH = Ranch Hand.
Comparison: Current Dioxin $\leq$ 10 ppt.
Background (Ranch Hand): Current Dioxin $\leq$ 10 ppt.
Low (Ranch Hand): Current Dioxin $>$ 10 ppt, 10 ppt $<$ Initial Dioxin $\leq$ 143 ppt.
High (Ranch Hand): Current Dioxin $>$ 10 ppt, Initial Dioxin $>$ 143 ppt.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20
(Zero vs. Nonzero)

g1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Zero/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	2.6 (116)	6.5 (107)	5.0 (121)	1.04 (0.73,1.47)	0.834
5	3.6 (112)	4.3 (116)	6.0 (116)	1.06 (0.78,1.44)	0.699
6[c]	3.6 (112)	4.3 (116)	6.0 (116)	1.03 (0.74,1.43)	0.883

h1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	344	1.02 (0.72,1.44)	0.912	PACKYR (p=0.054)
5	344	1.05 (0.78,1.42)	0.738	PACKYR (p=0.054)
6[d]	344	1.00 (0.72,1.39)	0.367	PACKYR (p=0.041)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-15. (Continued)
Analysis of Double Labelled Cells: CD5 with CD20 (cells/mm^3)
(Nonzero Measurements)

g2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	48.1 (113)	48.8 (100)	62.7 (115)	0.274	0.078 (0.033)	0.017
5	50.9 (108)	45.0 (111)	65.6 (109)	0.275	0.069 (0.028)	0.016
6[e]	51.7 (108)	45.1 (111)	64.7 (109)	0.276	0.062 (0.031)	0.044

h2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[af]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	48.2 (112)	51.8 (100)	60.0 (113)	0.321	0.063 (0.033)	0.060	AGE (p=0.012) ALC (p=0.002)
5	50.9 (107)	47.0 (111)	63.9 (107)	0.322	0.058 (0.029)	0.044	AGE (p=0.011) ALC (p=0.002)
6[e]	51.8 (107)	47.2 (111)	62.7 (107)	0.324	0.048 (0.031)	0.120	AGE (p=0.010) ALC (p=0.002)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD5 with CD20 versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covarites specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

The unadjusted analyses of Models 4 through 6 each displayed a significant positive association between nonzero CD5 with CD20 cell counts and current dioxin (Table 19-15(g2): p=0.017, p=0.016, and p=0.044 respectively). For Model 4, the unadjusted mean CD5 with CD20 cell counts for the low, medium, and high current dioxin categories were 48.1, 48.8, and 62.7 cells/mm^3; for Model 5 the corresponding means were 50.9, 45.0, and 65.6 cells/mm^3; and for Model 6 the means were 51.7, 45.1, and 64.7 cells/mm^3. Similarly, the adjusted analysis of Model 4 revealed a marginally significant positive association between nonzero CD5 with CD20 cell counts and Model 5 displayed a significant positive association (Table 19-15(h2): p=0.060 and p=0.044 respectively). The adjusted Model 4 means for the low, medium, and high current dioxin categories were 48.2, 51.8, and 60.0 cells/mm^3. Similarly, the Model 5 adjusted means were 50.9, 47.0, and 63.9 cells/mm^3. The adjusted Model 6 analysis was nonsignificant (p=0.120). Models 4 through 6 were adjusted for age and current alcohol use.

Double Labelled Cells: CD4 with CD8 Cells

Because 10.6 percent (90/849) of the CD4 with CD8 measurements were 0 cells/mm^3, the analysis was conducted in two parts. First, the proportion of CD4 with CD8 cell counts equal to 0 was examined for an association with exposure. Second, only nonzero measurements were explored for an association with exposure.

For the first analysis, no associations between the proportion of CD4 with CD8 measurement equal to zero and group, initial dioxin, or current dioxin were observed (Table 19-16(a1-h1): p>0.26). The Model 2 adjusted analysis did detect significant interactions between initial dioxin and race and between initial dioxin and current cigarette smoking (Table 19-16(d1): p=0.016 and p=0.028). Stratified analyses of these interactions are presented in Appendix Table O-2-12.

Similarly, the analysis based on nonzero CD4 with CD8 cell counts did not find any significant associations with group, initial, or current dioxin (Table 19-16(a2-h2): p>0.19 for all analyses). The Model 2 adjusted analysis detected a significant interaction between initial dioxin and lifetime alcohol history Table 19-16(d2): p=0.020), and the Model 3 adjusted analysis detected significant categorized dioxin-by-age, categorized dioxin-by-race and categorized dioxin-by-occupation interactions (Table 19-16(f2): p=0.001, p=0.031, and p=0.029 respectively). Stratified analyses of each of these interaction are presented in Appendix Table O-2-12.

Double Labelled Cells: CD3 with CD16+56 Cells

Because 3.4 percent (29/849) of the CD3 with CD16+56 measurements were 0 cells/mm^3, the analysis was conducted in two parts. First, the proportion of CD3 with CD16+56 cell counts equal to 0 was examined for an association with exposure. Second, only nonzero measurements were explored for an association with exposure.

For Model 1, no associations between the proportion of CD3 with CD16+56 cell counts equal to zero and group were observed (Table 19-17(a1,b1): p>0.32).

Table 19-16.
Analysis of Double Labelled Cells: CD4 with CD8
(Zero vs. Nonzero)

a1) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Zero**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***367***	***10.6***	***1.01 (0.65,1.56)***	***0.999***
	Comparison	***482***	***10.6***		
Officer	Ranch Hand	154	11.0	1.09 (0.54,2.20)	0.952
	Comparison	176	10.2		
Enlisted Flyer	Ranch Hand	66	9.1	1.98 (0.53,7.31)	0.480
	Comparison	83	4.8		
Enlisted Groundcrew	Ranch Hand	147	10.9	0.82 (0.43,1.56)	0.654
	Comparison	223	13.0		

b1) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.04 (0.67,1.62)***	***0.864***	AGE (p=0.005)
Officer	1.14 (0.56,2.30)	0.723	
Enlisted Flyer	2.12 (0.57,7.88)	0.263	
Enlisted Groundcrew	0.80 (0.42,1.54)	0.505	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8 (cells/mm^3)
(Nonzero Measurements)

a2) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[a]**	**Difference of Means (95% C.I.)[b]**	**p-Value[c]**
All	***Ranch Hand***	***328***	***30.0***	***-0.5 --***	***0.765***
	Comparison	***431***	***30.5***		
Officer	Ranch Hand	137	29.0	-1.6 --	0.498
	Comparison	158	30.6		
Enlisted Flyer	Ranch Hand	60	30.5	1.1 --	0.733
	Comparison	79	29.4		
Enlisted Groundcrew	Ranch Hand	131	30.9	0.1 --	0.946
	Comparison	194	30.8		

b2) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***328***	***30.0***	***-0.4 --***	0.769	AGE (p=0.059)
	Comparison	***430***	***30.4***			CSMOK (p<0.001)
Officer	Ranch Hand	137	28.9	-1.5 --	0.498	PACKYR (p=0.030)
	Comparison	158	30.4			
Enlisted Flyer	Ranch Hand	60	29.7	0.7 --	0.814	
	Comparison	79	29.0			
Enlisted Groundcrew	Ranch Hand	131	31.3	0.2 --	0.927	
	Comparison	193	31.1			

[a] Transformed from the 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-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

Note: Analysis based on measurements above 0 cells/mm^3 only.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8
(Zero vs. Nonzero)

c1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Zero	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	64	12.5	0.93 (0.65,1.33)	0.686
Medium	67	7.5		
High	72	13.9		

d1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
	Analysis Results for Log_2 (Initial Dioxin)[c]		
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
200	0.96 (0.68,1.37)**	0.829**	INIT*RACE (p=0.016) INIT*CSMOK (p=0.028) DRKYR (p=0.087)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-12 for further analysis of these interactions.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8 (cells/mm^3)
(Nonzero Measurements)

c2) 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	56	25.6	25.7	0.006	0.036 (0.037)	0.337
Medium	62	27.3	27.4			
High	62	28.7	28.6			

d2) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	56	26.4**	0.107	0.018 (0.037)**	0.628**	INIT*DRKYR (p=0.020) CSMOK (p=0.008)
Medium	60	27.5**				
High	61	27.1**				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of CD4 with CD8 versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-12 for further analysis of this interaction.

Note: Analysis based on measurements above 0 cells/mm^3 only.
Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8
(Zero vs. Nonzero)

e1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Zero	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	404	10.6		
Background RH	141	10.6	1.04 (0.55,1.96)	0.905
Low RH	95	10.5	1.03 (0.49,2.14)	0.945
High RH	108	12.0	1.04 (0.53,2.05)	0.902
Low plus High RH	203	11.3	1.04 (0.60,1.79)	0.900

f1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	404			AGE (p=0.017)
Background RH	141	1.15 (0.61,2.18)	0.671	
Low RH	95	1.18 (0.56,2.49)	0.662	
High RH	108	0.94 (0.48,1.86)	0.867	
Low plus High RH	203	1.04 (0.60,1.79)	0.893	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8 (cells/mm^3)
(Nonzero Measurements)

e2) 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	361	29.4	29.4		
Background RH	126	31.5	31.7	2.35 --	0.283
Low RH	85	26.5	26.4	-3.00 --	0.190
High RH	95	27.9	27.9	-1.46 --	0.518
Low plus High RH	180	27.2	27.2	-2.20 --	0.211

f2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ac]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	360	31.8**			DXCAT*AGE (p=0.001) DXCAT*RACE (p=0.029) DXCAT*OCC (p=0.031) CSMOK (p<0.001) PACKYR (p=0.042)
Background RH	126	34.8**	2.93 --**	0.230**	
Low RH	85	29.0**	-2.86 --**	0.251**	
High RH	95	29.7**	-2.10 --**	0.390**	
Low plus High RH	180	29.4**	-2.46 --**	0.192**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-12 for further analysis of these interactions.

Note: Analysis based on measurements above 0 cells/mm^3 only.
RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8
(Zero vs. Nonzero)

g1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Zero/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	9.5 (116)	12.1 (107)	11.6 (121)	1.02 (0.81,1.29)	0.852
5	10.7 (112)	9.5 (116)	12.9 (116)	1.03 (0.84,1.27)	0.763
6[c]	10.7 (112)	9.5 (116)	12.9 (116)	1.02 (0.81,1.27)	0.884

h1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	339	0.97 (0.76,1.23)	0.769	AGE (p=0.045) DRKYR (p=0.070)
5	339	0.98 (0.80,1.21)	0.882	AGE (p=0.048) DRKYR (p=0.068)
6[d]	339	0.96 (0.77,1.21)	0.736	AGE (p=0.044) DRKYR (p=0.067)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-16. (Continued)
Analysis of Double Labelled Cells: CD4 with CD8 (cells/mm^3)
(Nonzero Measurements)

g2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	31.3 (105)	27.6 (94)	27.8 (107)	0.002	-0.021 (0.027)	0.443
5	22.1 (112)	21.2 (116)	18.9 (116)	0.001	-0.021 (0.041)	0.614
6[d]	22.4 (112)	21.3 (116)	18.6 (116)	0.001	-0.028 (0.044)	0.522

h2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	30.7 (105)	27.9 (94)	28.2 (107)	0.083	-0.011 (0.027)	0.697	AGE (p=0.071) CSMOK (p<0.001) PACKYR (p=0.045)
5	21.6 (111)	20.1 (114)	19.6 (114)	0.063	0.005 (0.041)	0.906	AGE (p=0.021) CSMOK (p=0.001) DRKYR (p=0.103)
6[e]	22.0 (111)	20.2 (114)	19.2 (114)	0.064	-0.002 (0.044)	0.956	AGE (p=0.023) CSMOK (p=0.001) DRKYR (p=0.103)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of CD4 with CD8 versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-17.
Analysis of Double Labelled Cells: CD3 with CD16+56
(Zero vs. Nonzero)

a1) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Zero**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***367***	***3.8***	***1.24 (0.59,2.59)***	***0.713***
	Comparison	***482***	***3.1***		
Officer	Ranch Hand	154	3.9	0.85 (0.29,2.51)	0.985
	Comparison	176	4.5		
Enlisted Flyer	Ranch Hand	66	1.5	1.26 (0.08,20.56)	0.999
	Comparison	83	1.2		
Enlisted Groundcrew	Ranch Hand	147	4.8	1.81 (0.60,5.49)	0.441
	Comparison	223	2.7		

b1) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.29 (0.61,2.73)***	***0.503***	AGE (p=0.076) PACKYR (p=0.037)
Officer	0.94 (0.32,2.80)	0.913	
Enlisted Flyer	1.40 (0.09,22.86)	0.814	
Enlisted Groundcrew	1.75 (0.57,5.35)	0.325	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56 Cells (cells/mm^3)
(Nonzero Measurements)

a2) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Mean[ab]	Difference of Means (95% C.I.)[c]	p-Value[d]
All	***Ranch Hand***	***353***	***72.2***	***0.4 --***	***0.931***
	Comparison	***467***	***71.7***		
Officer	Ranch Hand	148	74.8	6.6 --	0.449
	Comparison	168	68.2		
Enlisted Flyer	Ranch Hand	65	77.3	12.3 --	0.424
	Comparison	82	65.0		
Enlisted Groundcrew	Ranch Hand	140	64.8	-8.1 --	0.465
	Comparison	217	72.9		

b2) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	Group	n	Adj. Mean[ae]	Difference of Adj. Means (95% C.I.)[c]	p-Value[d]	Covariate Remarks[f]
All	***Ranch Hand***	***350***	***91.5***	***-1.8 --***	0.771	AGE ($p<0.001$) RACE ($p<0.001$) CSMOK ($p=0.025$) ALC ($p=0.053$)
	Comparison	***463***	***93.3***			
Officer	Ranch Hand	148	98.1	4.8--	0.637	
	Comparison	167	93.3			
Enlisted Flyer	Ranch Hand	63	84.9	-5.0 --	0.720	
	Comparison	82	89.9			
Enlisted Groundcrew	Ranch Hand	139	88.9	-6.9 --	0.475	
	Comparison	214	95.8			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Note: Analysis based on measurements above 0 cells/mm^3 only.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56
(Zero vs. Nonzero)

c1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Zero	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	64	3.1	1.60 (0.95,2.70)	0.070
Medium	67	1.5		
High	72	8.3		

d1) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
203	****	****	INIT*OCC (p=0.005) PHYACT (p=0.046)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-13 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56 Cells (cells/mm^3)
(Nonzero Measurements)

c2) 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	62	79.0	81.6	0.438	-0.138 (0.071)	0.055
Medium	66	77.7	81.0			
High	66	60.0	58.3			

d2) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	62	121.1	0.523	-0.129 (0.081)	0.115	OCC (p=0.076)
Medium	64	122.4				RACE (p=0.066) CSMOK (p=0.022)
High	65	94.4				PACKYR (p=0.035) DRKYR (p=0.006)

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of CD3 with CD16+56 versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56
(Zero vs. Nonzero)

e1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Zero	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	404	3.5		
Background RH	141	2.8	0.79 (0.25,2.47)	0.685
Low RH	95	2.1	0.62 (0.14,2.78)	0.529
High RH	108	6.4	1.92 (0.74,4.96)	0.177
Low plus High RH	203	4.4	1.30 (0.55,3.07)	0.553

f1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	403			PACKYR (p=0.033)
Background RH	141	0.77 (0.25,2.41)	0.652	
Low RH	95	0.70 (0.15,3.17)	0.642	
High RH	108	1.85 (0.71,4.81)	0.204	
Low plus High RH	203	1.35 (0.57,3.20)	0.501	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56 Cells (cells/mm^3)
(Nonzero Measurements)

e2) 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	390	72.2	72.1		
Background RH	137	77.6	78.8	6.7 --	0.355
Low RH	93	78.9	78.3	6.2 --	0.458
High RH	101	62.4	62.0	-10.1 --	0.158
Low plus High RH	194	69.8	69.3	-2.8 --	0.645

f2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	387	100.9			AGE (p=0.002) RACE (p<0.001) CSMOK (p=0.089) ALC (p=0.004)
Background RH	136	106.0	5.1 --	0.603	
Low RH	93	101.3	0.4 --	0.974	
High RH	99	85.0	-15.9 --	0.103	
Low plus High RH	192	92.5	-8.4 --	0.294	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56
(Zero vs. Nonzero)

g1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[a]	Current Dioxin Category Percent Zero/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) Est. Relative Risk (95% C.I.)[b]	p-Value
4	2.6 (116)	2.8 (107)	5.8 (121)	1.53 (1.06,2.22)	0.024
5	2.7 (112)	1.7 (116)	6.9 (116)	1.56 (1.11,2.21)	0.010
6[c]	2.7 (112)	1.7 (116)	6.9 (116)	1.46 (1.01,2.10)	0.042

h1) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[a]	n	Analysis Results for Log_2 (Current Dioxin + 1) Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	344	****	****	CURR*PHYACT (p=0.004)
5	344	****	****	CURR*PHYACT (p=0.008)
6[d]	344	****	****	CURR*PHYACT (p=0.008)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

**** Log_2 (current dioxin + 1)-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-13 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-17. (Continued)
Analysis of Double Labelled Cells: CD3 with CD16+56 Cells (cells/mm^3)
(Nonzero Measurements)

g2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[c]	Current Dioxin Category Mean[ab]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Slope (Std. Error)[d]	p-Value
4	83.4 (113)	82.1 (104)	56.6 (114)	0.302	-0.102 (0.041)	0.014
5	85.6 (109)	75.8 (114)	58.9 (108)	0.304	-0.093 (0.035)	0.009
6[e]	82.0 (109)	75.5 (114)	60.6 (108)	0.308	-0.074 (0.038)	0.053

h2) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[c]	Current Dioxin Category Adjusted Mean[af]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	101.9 (112)	96.9 (104)	71.1 (112)	0.339	-0.086 (0.042)	0.040	AGE (p=0.056) RACE (p=0.038) ALC (p=0.009)
5	106.7 (108)	90.3 (114)	76.3 (106)	0.340	-0.077 (0.036)	0.032	AGE (p=0.052) RACE (p=0.041) ALC (p=0.010)
6[e]	101.6 (108)	88.8 (114)	77.3 (106)	0.343	-0.060 (0.039)	0.122	AGE (p=0.043) RACE (p=0.054) ALC (p=0.010)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of CD3 with CD16+56 Cells versus log_2 (current dioxin).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Analysis based on measurements above 0 cells/mm^3 only.
Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Based on the nonzero CD3 with CD16+56 cells counts, the Model 1 unadjusted and adjusted analyses were nonsignificant (Table 19-17(a2,b2): $p>0.42$ for all analyses).

The unadjusted Model 2 analysis of the dichotomized CD3 with CD16+56 cell counts revealed a marginally significant positive association with initial dioxin (Table 19-17(c1): $p=0.070$, Est. RR=1.60). The adjusted Model 2 analysis displayed a highly significant interaction between initial dioxin and occupation (Table 19-17(d1): $p=0.005$). Model 2 also was adjusted for the physical activity index. Stratified analyses of the interaction with occupation revealed a significant positive association between initial dioxin and the proportion of zero CD3 with CD16+56 cell counts for the enlisted groundcrew (Appendix Table O-2-13(a): $p=0.048$, Adj. RR=2.30). The percentages of zero CD3 with CD16+56 cell counts for the low, medium, and high initial dioxin categories of enlisted groundcrew were 0.0, 2.8, and 0.2 percent.

The unadjusted Model 2 analysis of the nonzero CD3 with CD16+56 cell counts revealed a marginally significant inverse association with initial dioxin (Table 19-17(c2): $p=0.055$). The mean cell counts, adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, were lowest for Ranch Hands in the high initial dioxin category (low = 81.6 cells/mm^3, medium = 81.0 cells/mm^3, and high = 58.3 cells/mm^3). After adjusting Model 2 for occupation, race, current cigarette smoking, lifetime cigarette smoking history, and lifetime alcohol history, the association between CD3 with CD16+56 cell counts and initial dioxin was nonsignificant (Table 19-17(d2): $p=0.115$). When occupation was removed from the final adjusted model, the association became significant (Appendix Table O-3-13(b): $p=0.004$).

The Model 3 unadjusted and adjusted analyses of the proportion of zero CD3 with CD16+56 cell counts did not find any significant associations with categorized dioxin (Table 19-17(e1,f1): $p>0.17$). The adjusted Model 3 analysis accounted for lifetime cigarette smoking history.

Both the unadjusted and adjusted Model 3 analyses of the nonzero CD3 with CD16+56 cell counts were nonsignificant (Table 19-17(e2,f2): $p>0.10$). Model 3 was adjusted for age, race, current cigarette smoking, and current alcohol use.

The unadjusted analyses of Models 4 through 6 revealed significant positive associations between the proportion of zero CD3 with CD16+56 cell counts and current dioxin (Table 19-17(g1): $p=0.024$, Est. RR=1.53; $p=0.010$, Est. RR=1.56; and $p=0.042$, Est. RR=1.46). The percentages of zero CD3 with CD16+56 cell counts for the low, medium, and high current dioxin categories were 2.6, 2.8, and 5.8 percent for Model 4, and 2.7, 1.7, and 6.9 percent for Models 5 and 6. The adjusted analyses of Models 4 through 6 each exhibited a highly significant current dioxin-by-physical activity index interaction (Table 19-17(h1): $p=0.004$, $p=0.008$, and $p=0.008$ respectively). Stratified analyses of these interactions display highly significant positive associations between the proportion of zero CD3 with CD16+56 cell counts and current dioxin for sedentary Ranch Hands (Appendix Table O-2-13(b-d): $p=0.002$, $p=0.001$, and $p=0.003$ for Models 4, 5, and 6). The percentages of zero CD3 with CD16+56 cell counts for sedentary Ranch Hands in the

low, medium, and high current dioxin categories were 0.0, 2.0, and 7.7 percent for Model 4, and 0.0, 1.9, and 8.1 percent for Models 5 and 6.

The unadjusted analyses of Models 4 through 6 revealed significant and marginally significant inverse associations between the nonzero CD3 with CD16+56 cell counts and current dioxin (Table 19-17(g2): $p=0.014$, $p=0.009$, and $p=0.053$ for Models 4, 5, and 6). The mean CD3 with CD16+56 cell counts decreased with increasing levels of current dioxin (Model 4: low = 83.4, medium = 82.1, and high = 56.6 cells/mm^3; Model 5: low = 85.6, medium = 75.8, and high = 58.9 cells/mm^3; Model 6: low = 82.0, medium = 75.5, and high = 60.6 cells/mm^3). Similarly, the adjusted analysis of Models 4 and 5 revealed significant inverse associations between nonzero CD3 with CD16+56 cell counts (Table 19-17(h2): $p=0.040$ and $p=0.032$ respectively). The adjusted Model 4 means for the low, medium, and high current dioxin categories were 101.9, 96.9, and 71.1 cells/mm^3. Similarly, the Model 5 adjusted means were 106.7, 90.3, and 76.3 cells/mm^3. The adjusted Model 6 analysis was nonsignificant ($p=0.122$). Models 4 through 6 each were adjusted for age, race, and current alcohol use.

Total Lymphocyte Count

The unadjusted and adjusted Model 1 analyses of total lymphocyte count revealed no significant differences between Ranch Hands and Comparisons (Table 19-18(a,b): $p>0.12$ for all contrasts). Occupation and current cigarette smoking were significant covariates in the adjusted model.

The unadjusted Model 2 and Model 3 unadjusted analyses showed no significant associations between dioxin and total lymphocyte count (Table 19-18(c,e): $p>0.28$ for all analyses). A highly significant interaction between initial dioxin and the physical activity index was present in the adjusted analysis of Model 2 (Table 19-18(d): $p=0.009$). A categorized dioxin-by-age interaction was significant in the adjusted analysis of Model 3 (Table 19-18(f): $p=0.046$). Stratified analyses of these interactions are presented in Appendix Table O-2-14. The adjusted Model 3 analysis, after the categorized dioxin-by-age interaction was removed, displayed no significant results (Table 19-18(f): $p>0.50$ for all contrasts). Age and current cigarette smoking were included in the adjusted Model 2 analysis. In Model 3, current cigarette smoking and current alcohol use were retained.

There were no significant associations between current dioxin and total lymphocyte count in the unadjusted and adjusted analyses of Models 4, 5, and 6 (Table 19-18 (g,h): $p>0.56$ for all analyses). Current cigarette smoking was a significant covariate in the adjusted analyses of Models 4, 5, and 6. Current alcohol use also was included in the Model 6 adjusted analysis.

IgA

Analysis of IgA did not reveal a significant difference in means between Ranch Hands and Comparisons in either the unadjusted or adjusted analyses of Model 1 (Table 19-19(a,b):$p>0.52$ for all unadjusted and adjusted analyses). The covariates age, occupation, and current alcohol use were retained for in the final adjusted model.

Table 19-18.
Analysis of TLC (cells/mm^3)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Mean[ab]**	**Difference of Means (95% C.I.)[c]**	**p-Value[d]**
All	***Ranch Hand***	***367***	***2,059.4***	***9.3 --***	***0.851***
	Comparison	***482***	***2,050.1***		
Officer	Ranch Hand	154	2,002.3	121.2 --	0.129
	Comparison	176	1,881.1		
Enlisted Flyer	Ranch Hand	66	2,002.4	-105.6 --	0.531
	Comparison	83	2,108.0		
Enlisted Groundcrew	Ranch Hand	147	2,175.3	75.3 --	0.373
	Comparison	223	2,100.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[ae]**	**Difference of Adj. Means (95% C.I.)[c]**	**p-Value[d]**	**Covariate Remarks[f]**
All	***Ranch Hand***	***367***	***2,063.9***	***20.1 --***	0.672	OCC (p=0.037)
	Comparison	***481***	***2,043.8***			CSMOK (p<0.001)
Officer	Ranch Hand	154	2,021.4	59.5 --	0.413	
	Comparison	176	1,961.9			
Enlisted Flyer	Ranch Hand	66	1,974.4	-134.4 --	0.230	
	Comparison	83	2,108.8			
Enlisted Groundcrew	Ranch Hand	147	2,152.6	48.1 --	0.525	
	Comparison	222	2,104.5			

[a] Transformed from the natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[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-values based on difference of means on natural logarithm scale.

[e] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

[f] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-18. (Continued)
Analysis of TLC (cells/mm^3)

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	64	1,914.3	1,941.7	0.452	0.024 (0.022)	0.282
Medium	67	2,036.6	2,070.0			
High	72	2,176.2	2,142.0			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	64	****	0.578	****	****	INIT*PHYACT (p=0.009)
Medium	67	****				AGE (p=0.061)
High	72	****				CSMOK (p<0. 001)

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

[c] Slope and standard error based on natural logarithm of TLC versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

**** Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, and p-value not presented; refer to Appendix Table O-2-14 for further analysis of this interaction.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-18. (Continued)
Analysis of TLC (cells/mm^3)

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	404	2,022.0	2,021.7		
Background RH	141	2,054.3	2,059.2	37.5 --	0.587
Low RH	95	1,949.3	1,956.9	-64.8 --	0.409
High RH	108	2,073.9	2,065.1	43.4 --	0.568
Low plus High RH	203	2,014.6	2,013.7	-8.0 --	0.894

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	400	2,022.4**			DXCAT*AGE (p=0.046) CSMOK (p<0.001) ALC (p=0.139)
Background RH	140	2,066.7**	44.3 --**	0.507**	
Low RH	95	1,998.6**	-23.8 --**	0.757**	
High RH	106	2,034.4**	12.0 --**	0.870**	
Low plus High RH	201	2,017.4**	-5.0 --**	0.931**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and examination group (batch-to-batch) variation.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, examination group (batch-to-batch) variation, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-14 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-18. (Continued)
Analysis of TLC (cells/mm^3)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[ab]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[c]	Low	Medium	High	R^2	Slope (Std. Error)[d]	p-Value
4	2,033.3 (116)	2,002.2 (107)	2,048.6 (121)	0.269	0.005 (0.014)	0.702
5	2,045.9 (112)	1,960.1 (116)	2,087.1 (116)	0.270	0.005 (0.012)	0.657
6[e]	2,070.2 (112)	1,962.9 (116)	2,067.5 (116)	0.274	-0.001 (0.013)	0.957

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[c]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[d]	p-Value	Covariate Remarks
4	2,025.8 (116)	2,035.4 (107)	2,037.8 (121)	0.352	0.005 (0.013)	0.684	CSMOK ($p<0.001$)
5	2,042.2 (112)	1,983.1 (116)	2,079.4 (116)	0.352	0.006 (0.011)	0.566	CSMOK ($p<0.001$)
6[e]	2,064.7 (111)	1,988.3 (116)	2,068.0 (114)	0.361	0.002 (0.012)	0.869	CSMOK ($p<0.001$) ALC ($p=0.148$)

[a] Transformed from natural logarithm scale.

[b] Adjusted for examination group (batch-to-batch) variation.

[c] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[d] Slope and standard error based on natural logarithm of TLC versus log_2 (current dioxin + 1).

[e] Adjusted for log_2 total lipids.

[f] Adjusted for examination group (batch-to-batch) variation and covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-19.
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]**
All	***Ranch Hand***	***936***	***217.2***	***-1.2 --***	***0.787***
	Comparison	***1,264***	***218.4***		
Officer	Ranch Hand	363	211.4	-2.7 --	0.701
	Comparison	492	214.1		
Enlisted Flyer	Ranch Hand	160	214.0	-0.8 --	0.943
	Comparison	200	214.8		
Enlisted Groundcrew	Ranch Hand	413	223.6	0.3 --	0.962
	Comparison	572	223.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***926***	***215.5***	***-1.5 --***	0.729	AGE ($p<0.001$)
	Comparison	***1,246***	***217.0***			OCC ($p=0.001$)
Officer	Ranch Hand	363	206.4	-4.3 --	0.528	ALC ($p=0.063$)
	Comparison	485	210.7			
Enlisted Flyer	Ranch Hand	157	212.8	0.7 --	0.954	
	Comparison	200	212.1			
Enlisted Groundcrew	Ranch Hand	406	228.4	0.3 --	0.970	
	Comparison	561	228.1			

[a] Transformed from the 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-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-19. (Continued)
Analysis of IgA (mg/dl)

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	171	213.4	213.2	0.010	0.020 (0.016)	0.211
Medium	172	221.8	222.3			
High	168	222.7	222.5			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	171	234.3	0.035	0.032 (0.016)	0.052	AGE (p=0.080) RACE (p=0.001)
Medium	172	249.1				
High	168	253.5				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of IgA versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-19. (Continued)
Analysis of IgA (mg/dl)

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	1,051	220.4	220.4		
Background RH	367	214.6	216.5	-3.9 --	0.529
Low RH	256	216.9	215.6	-4.8 --	0.490
High RH	255	221.6	220.2	-0.2 --	0.987
Low plus High RH	511	219.3	217.8	-2.6 --	0.648

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	1,051	228.2**			DXCAT*RACE (p=0.027) AGE (p<0.001) OCC (p=0.009)
Background RH	367	226.4**	-1.8 --**	0.780**	
Low RH	256	221.7**	-6.5 --**	0.365**	
High RH	255	226.2**	-2.0 --**	0.795**	
Low plus High RH	511	224.0**	-4.2 --**	0.453**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-15 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-19. (Continued)
Analysis of IgA (mg/dl)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	213.1 (289)	217.4 (295)	221.4 (294)	0.002	0.013 (0.011)	0.218
5	213.4 (294)	221.5 (292)	217.1 (292)	0.001	0.007 (0.009)	0.455
6[d]	210.1 (293)	221.3 (292)	220.0 (292)	0.006	0.016 (0.010)	0.099

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	230.5 (289)	229.3 (295)	232.0 (294)	0.026	0.008 (0.012)	0.530	AGE ($p<0.001$) OCC ($p=0.046$) RACE ($p=0.027$)
5	230.7 (294)	233.0 (292)	225.8 (292)	0.025	0.001 (0.010)	0.945	AGE ($p<0.001$) OCC ($p=0.023$) RACE ($p=0.030$)
6[e]	225.7 (292)	232.0 (292)	229.8 (292)	0.033	0.014 (0.011)	0.202	AGE ($p=0.001$) OCC ($p=0.064$) RACE ($p=0.027$) PACKYR ($p=0.098$)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of IgA versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

The unadjusted analysis of Model 2 did not reveal any significant results (Table 19-19(c): $p=0.211$). The adjusted analysis, however, showed a marginally significant positive association between IgA and initial dioxin (Table 19-19(d): $p=0.052$, Slope=0.032). The adjusted means in the low, medium, and high initial dioxin categories are 234.3 mg/dl, 249.1 mg/dl, and 253.5 mg/dl respectively. Age and race were included in the final adjusted model of Model 2.

The unadjusted analysis of Model 3 did not show a significant relationship between categorized dioxin and IgA (Table 19-19(e): $p \geq 0.49$ for all unadjusted contrasts). However, adjusting for covariates revealed a significant categorized dioxin-by-race interaction (Table 19-19(f): $p=0.027$). Age and occupation also were significant in the final model. Removal of the interaction showed no significant association between categorized dioxin and IgA (Table 19-19(f): $p>0.36$ for all adjusted contrasts). Stratified results of the categorized dioxin-by-race interaction are displayed in Appendix Table O-2-15.

Models 4 and 5 showed no significant relationships between IgA and current dioxin in the unadjusted and adjusted analyses (Table 19-19(g,h): $p>0.21$ for unadjusted and adjusted analyses). Age, occupation, and race were significant in each of the final adjusted models of Models 4 and 5. After excluding occupation from the final model in Model 4, the results became marginally significant (Appendix Table O-3-14(b): $p=0.062$, Slope=0.020). The unadjusted analysis of Model 6 showed a marginally significant association between current dioxin and IgA (Table 19-19(g): $p=0.099$, Slope=0.016). The unadjusted means in the low, medium, and high current dioxin categories were 210.1 mg/dl, 221.3 mg/dl, and 220.0 mg/dl respectively. The adjusted analysis of Model 6 did not reveal a significant relationship between IgA and current dioxin (Table 19-19(h): $p=0.202$). Covariates in the final adjusted model were age, occupation, race, and lifetime cigarette smoking history. After excluding occupation from the final adjusted model of Model 6, a significant positive relationship between IgA and current lipid-adjusted dioxin was revealed (Appendix Table O-3-14(b): $p=0.019$, Slope=0.024).

IgG

The unadjusted analysis of Model 1 displayed a marginally significant difference in mean IgG values between Ranch Hands (1,032.1 mg/dl) and Comparisons (1,051.7 mg/dl) (Table 19-20(a): $p=0.058$). Similarly, the adjusted analysis of Model 1 revealed a marginally significant difference in means between Ranch Hands and Comparisons (Table 19-20(b): $p=0.092$). The adjusted means for Ranch Hands and Comparisons were 1,123.2 mg/dl and 1,141.5 mg/dl. Age, occupation, race, current cigarette smoking, and lifetime cigarette smoking history were significant in the final adjusted model.

The Model 2 unadjusted and adjusted analyses of IgG were nonsignificant (Table 19-20(c,d): $p>0.55$ for unadjusted and adjusted analyses). Occupation, race, current cigarette smoking, and current alcohol use were included in the adjusted analysis. The unadjusted analysis of Model 3 did not reveal a significant relationship between IgG and categorized dioxin (Table 19-20(e): $p>0.14$ for all unadjusted analyses). After adjusting for covariates in Model 3, a significant interaction between categorized dioxin and occupation was revealed (Table 19-20(f): $p=0.024$). Age, race, current cigarette smoking, lifetime cigarette smoking

Table 19-20.
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]**
All	***Ranch Hand***	***936***	***1,032.1***	***-19.6 --***	***0.058***
	Comparison	***1,264***	***1,051.7***		
Officer	Ranch Hand	363	1,014.5	-22.1 --	0.157
	Comparison	492	1,036.6		
Enlisted Flyer	Ranch Hand	160	1,003.7	-43.0 --	0.104
	Comparison	200	1,046.7		
Enlisted Groundcrew	Ranch Hand	413	1,059.2	-7.4 --	0.643
	Comparison	572	1,066.6		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***935***	***1,123.2***	***-18.3 --***	0.092	AGE (p=0.010)
	Comparison	***1,262***	***1,141.5***			OCC (p=0.001)
Officer	Ranch Hand	362	1,101.2	-23.5 --	0.169	RACE (p<0.001)
	Comparison	492	1,124.7			CSMOK (p<0.001)
Enlisted Flyer	Ranch Hand	160	1,100.6	-41.1 --	0.119	PACKYR (p=0.029)
	Comparison	200	1,141.7			
Enlisted Groundcrew	Ranch Hand	413	1,160.6	-4.8 --	0.770	
	Comparison	570	1,165.4			

[a] Transformed from the 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-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-20. (Continued)
Analysis of IgG (mg/dl)

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	171	1,035.4	1,035.2	0.001	0.005 (0.008)	0.551
Medium	172	1,045.2	1,045.3			
High	168	1,028.3	1,028.3			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	169	1,134.1	0.109	-0.001 (0.009)	0.943	OCC (p=0.057) RACE (p<0.001) CSMOK (p=0.002) ALC (p=0.015)
Medium	169	1,141.3				
High	166	1,101.3				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of IgG versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-20. (Continued)
Analysis of IgG (mg/dl)

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	1,051	1,051.8	1,051.7		
Background RH	367	1,026.8	1,030.4	-21.3 --	0.140
Low RH	256	1,036.4	1,035.0	-16.8 --	0.310
High RH	255	1,036.2	1,033.0	-18.7 --	0.258
Low plus High RH	511	1,036.3	1,034.0	-17.7 --	0.165

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	1,035	1,138.7**			DXCAT*OCC (p=0.024)
Background RH	364	1,126.9**	-11.8 --**	0.451**	AGE (p=0.097) RACE (p<0.001) CSMOK (p<0.001) PACKYR (p=0.143) ALC (p=0.123)
Low RH	253	1,111.2**	-27.5 --**	0.112**	
High RH	251	1,115.1**	-23.6 --**	0.189**	
Low plus High RH	504	1,113.1**	-25.6 --**	0.060**	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-16 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-20. (Continued)
Analysis of IgG (mg/dl)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[b]	Current Dioxin Category Mean[a]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Slope (Std. Error)[c]	p-Value
4	1,027.1 (289)	1,020.9 (295)	1,049.1 (294)	0.001	0.004 (0.005)	0.508
5	1,031.2 (294)	1,028.1 (292)	1,037.7 (292)	<0.001	-0.001 (0.005)	0.892
6[d]	1,018.9 (293)	1,027.1 (292)	1,051.2 (292)	0.012	0.005 (0.005)	0.290

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[b]	Current Dioxin Category Adjusted Mean[a]/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	1,133.1 (288)	1,114.0 (292)	1,135.1 (289)	0.085	-0.003 (0.006)	0.598	OCC (p=0.038) RACE (p<0.001) CSMOK (p<0.001) ALC (p=0.021)
5	1,137.2 (292)	1,119.5 (290)	1,121.2 (287)	0.086	-0.007 (0.005)	0.206	OCC (p=0.018) RACE (p<0.001) CSMOK (p<0.001) ALC (p=0.024)
6[e]	1,123.7 (291)	1,115.8 (290)	1,129.7 (287)	0.091	-0.002 (0.006)	0.714	OCC (p=0.030) RACE (p<0.001) CSMOK (p<0.001) ALC (p=0.033)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of IgG versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

history, and current alcohol use also were retained in the final adjusted model. Removal of the interaction exhibited a significant difference in means between the low plus high Ranch Hand category (1,113.1 mg/dl) and the Comparisons (1,138.7 mg/dl) (Table 19-20(f): $p=0.060$). After excluding occupation from the final model, this contrast became nonsignificant (Appendix Table O-3-15(b): $p=0.104$). Additionally, the contrast between low Ranch Hands and Comparisons became marginally significant after occupation was removed from the final model: $p=0.096$).

The unadjusted and adjusted analysis of Models 4 through 6 did not reveal any significant associations between current dioxin and IgG (Table 19-20(g,h): $p>0.20$ for all unadjusted and adjusted analyses). Occupation, race, current cigarette smoking, and current alcohol use were significant in each of the final adjusted models.

IgM

The Model 1 unadjusted analyses of IgM did not reveal any significant associations between Ranch Hands and Comparisons (Table 19-21(a): $p>0.14$). The adjusted analyses revealed a significant group-by-race interaction and a group-by-physical activity index interaction (Table 19-21(b): $p=0.034$ and $p=0.005$ respectively). Removal of these interactions did not reveal a significant difference in mean IgM values between Ranch Hands and Comparisons (Table 19-21(b): $p>0.12$ for adjusted analyses). Age and current alcohol also were significant in the final adjusted model. Stratified tables of the interactions are displayed in Appendix Table O-2-17.

The Model 2 unadjusted and adjusted analyses did not reveal any significant associations between initial dioxin and IgM (Table 19-21(c,d): $p>0.14$ for unadjusted and adjusted analysis). Age, race, occupation, and the physical activity index were included in the final adjusted model. The unadjusted analysis of Model 3 did not reveal a significant relationship between categorized dioxin and IgM (Table 19-21(e): $p>0.58$). Adjusting for covariates in Model 3 revealed a highly significant interaction between categorized dioxin and physical activity index (Table 19-21(f): $p=0.001$). Stratified results of this interaction are shown in Appendix Table O-2-17. Very active Ranch Hands had significantly higher IgM values than Comparisons, while sedentary and moderately active Ranch Hands generally had slightly lower IgM values than Comparisons. Age, race, and current alcohol use also were significant in the final adjusted model.

The unadjusted analysis of IgM for Models 4 through 6 did not reveal any significant associations with current dioxin (Table 19-21(g): $p>0.69$). The adjusted analysis of Model 4 revealed a significant current dioxin-by-current alcohol use interaction (Table 19-21(h): $p=0.033$). Age, race, and the physical activity index also were significant in the final model. Removal of the interaction did not reveal any significant findings. Stratified results of the current dioxin-by-current alcohol use interaction are presented in Appendix Table O-2-17. Models 5 and 6 did not reveal any significant results in the adjusted analysis (Table 19-21(h): $p>0.68$). Age, race, current alcohol use, and the physical activity index were significant in Models 5 and 6.

Table 19-21.
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]**
All	***Ranch Hand***	***936***	***103.9***	***-1.6 --***	***0.498***
	Comparison	***1,264***	***105.5***		
Officer	Ranch Hand	363	104.3	0.9 --	0.825
	Comparison	492	103.4		
Enlisted Flyer	Ranch Hand	160	100.3	-9.2 --	0.141
	Comparison	200	109.5		
Enlisted Groundcrew	Ranch Hand	413	104.9	-1.2 --	0.748
	Comparison	572	106.1		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED						
Occupational Category	**Group**	**n**	**Adj. Mean[a]**	**Difference of Adj. Means (95% C.I.)[b]**	**p-Value[c]**	**Covariate Remarks[d]**
All	***Ranch Hand***	***926***	***97.0*****	***-1.3 --*****	0.579**	GROUP*RACE (p=0.034)
	Comparison	***1,246***	***98.3*****			GROUP*PHYACT (p=0.005)
Officer	Ranch Hand	363	98.1**	0.6 --**	0.868**	AGE (p<0.001)
	Comparison	485	97.5**			ALC (p=0.019)
Enlisted Flyer	Ranch Hand	157	94.2**	-8.8 --**	0.127**	
	Comparison	200	103.0**			
Enlisted Groundcrew	Ranch Hand	406	97.2**	-0.2 --**	0.950**	
	Comparison	561	97.4**			

[a] Transformed from the 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-values based on difference of means on natural logarithm scale.

[d] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interactions ($p \leq 0.05$); adjusted mean, difference of adjusted means, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-17 for further analysis of these interactions.

Table 19-21. (Continued)
Analysis of IgM (mg/dl)

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	171	100.1	99.8	0.004	0.023 (0.019)	0.230
Medium	172	99.4	99.1			
High	168	107.7	108.2			

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED						
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[d]			
Initial Dioxin	n	Adj. Mean[ad]	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
Low	171	93.7	0.057	0.032 (0.022)	0.145	AGE (p=0.021) RACE (p=0.089) OCC (p=0.055) PHYACT (p=0.002)
Medium	172	96.0				
High	168	104.7				

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Slope and standard error based on natural logarithm of IgM versus log_2 (initial dioxin).

[d] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-21. (Continued)
Analysis of IgM (mg/dl)

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	1,051	104.8	104.8		
Background RH	367	106.7	105.4	0.6 --	0.863
Low RH	256	102.0	102.7	-2.1 --	0.610
High RH	255	102.5	103.4	-1.4 --	0.731
Low plus High RH	511	102.3	103.1	-1.7 --	0.581

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Mean[ae]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]	Covariate Remarks
Comparison	1,035	****			DXCAT*PHYACT (p=0.001) AGE (p=0.015) RACE (p=0.002) ALC (p=0.023)
Background RH	365	****	****	****	
Low RH	253	****	****	****	
High RH	251	****	****	****	
Low plus High RH	504	****	****	****	

[a] Transformed from natural logarithm scale.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

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

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

[e] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Categorized dioxin-by-covariate interaction ($p \leq 0.01$); adjusted mean, difference of adjusted means, and p-value not presented; refer to Appendix Table O-2-17 for further analysis of this interaction.

Table 19-21. (Continued)
Analysis of IgM (mg/dl)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED						
	Current Dioxin Category Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)		
Model[b]	Low	Medium	High	R^2	Slope (Std. Error)[c]	p-Value
4	105.8 (289)	104.8 (295)	101.7 (294)	<0.001	0.001 (0.013)	0.914
5	105.3 (294)	105.6 (292)	101.4 (292)	<0.001	-0.002 (0.011)	0.825
6[d]	104.0 (293)	105.4 (292)	103.1 (292)	0.005	0.005 (0.012)	0.698

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED							
	Current Dioxin Category Adjusted Mean[a]/(n)			Analysis Results for Log_2 (Current Dioxin + 1)			
Model[b]	Low	Medium	High	R^2	Adj. Slope (Std. Error)[c]	p-Value	Covariate Remarks
4	95.2** (288)	96.5** (292)	91.4** (289)	0.038	-0.001 (0.013)**	0.954**	CURR*ALC (p=0.033) AGE (p=0.011) RACE (p=0.001) PHYACT (p=0.016)
5	94.7 (292)	96.9 (290)	91.0 (287)	0.033	-0.005 (0.011)	0.685	AGE (p=0.009) RACE (p=0.001) ALC (p=0.041) PHYACT (p=0.015)
6[e]	92.7 (291)	96.2 (290)	92.3 (287)	0.039	0.004 (0.012)	0.761	AGE (p=0.019) RACE (p=0.001) ALC (p=0.027) PHYACT (p=0.016)

[a] Transformed from natural logarithm scale.

[b] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[c] Slope and standard error based on natural logarithm of IgM versus log_2 (current dioxin + 1).

[d] Adjusted for log_2 total lipids.

[e] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-17 for further analysis of this interaction.

Lupus Panel: Antinuclear Antibody (ANA)

The Model 1 unadjusted analysis of the antinuclear antibody (ANA) revealed a marginally significant difference between Ranch Hands and Comparisons (Table 19-22(a): $p=0.092$, Est. RR=0.81). The analysis of ANA yielded positive results for 13.7 percent of Ranch Hands and 16.4 percent of Comparisons. Stratifying by occupation also revealed a marginally significant difference between Ranch Hands and Comparisons in the enlisted groundcrew category (Table 19-22(a): $p=0.073$, Est. RR=0.69). Within the enlisted groundcrew category, 10.9 percent of Ranch Hands and 15.0 percent of Comparisons yielded positive ANA results. Similar to the unadjusted analysis, the Model 1 adjusted analysis revealed a marginally significant difference between Ranch Hands and Comparisons overall and for the enlisted groundcrew (Table 19-22(b): $p=0.067$, Adj. RR=0.80 and $p=0.058$, Adj. RR=0.069 respectively). Age was significant in the final adjusted model.

Model 2 did not display a significant association between initial dioxin and ANA (Table 19-22(c,d): $p>0.59$ for both the unadjusted and adjusted analyses). Age, race, and lifetime alcohol history were significant in the final adjusted model. In Model 3, the unadjusted analysis exhibited a significantly lower percentage of positive ANA results in the high Ranch Hand category (11.4%) and low plus high Ranch Hand combined category (13.1%) than in Comparisons (17.1%) (Table 19-22(e): $p=0.030$, Est. RR=0.63 and 0.047, Est. RR=0.73, respectively). Adjusting for covariates in Model 3 revealed a highly significant categorized dioxin-by-lifetime alcohol history interaction (Table 19-22(f): $p=0.002$). Age also was significant in the final adjusted model. Stratified results of the interaction between lifetime alcohol history and categorized dioxin are presented in Appendix Table O-2-18.

The unadjusted analyses of Models 4 and 5 did not reveal any significant relationships between current dioxin and ANA (Table 19-22(g): $p>0.13$). The unadjusted analysis of Model 6 revealed a marginally significant inverse relationship between ANA and current dioxin (Table 19-22(g): $p=0.099$, Est. RR=0.90). Adjusting for covariates in Models 4 through 6 revealed significant current dioxin-by-race and current dioxin-by-lifetime alcohol history interactions in each model (Table 19-22(h): Model 4, $p=0.023$ and $p=0.002$; Model 5, $p=0.014$ and $p=0.003$; Model 6, $p=0.016$ and $p=0.003$). Age also was significant in the final adjusted model of Models 4 through 6. Removal of the interactions did not reveal any significant associations between current dioxin and ANA. Stratified results of the current dioxin-by-race and current dioxin-by-lifetime alcohol history interactions for Models 4, 5, and 6 are presented in Appendix Table O-2-18.

Lupus Panel: Thyroid Microsomal Antibody

Model 1 revealed a marginally significant overall difference between Ranch Hands and Comparisons in the unadjusted analysis of the thyroid microsomal antibody (Table 19-23(a): $p=0.054$, Est. RR=1.61). The results were positive for 4.4 percent of Ranch Hands and 2.8 percent of Comparisons. Adjusting for covariates in Model 1 revealed three highly significant interactions: group-by-current cigarette smoking, group-by-current alcohol use, and group-by-lifetime alcohol history (Table 19-23(b): $p=0.001$, $p=0.002$, and $p<0.001$ respectively). The physical activity index also was included in the final adjusted model. For further investigation, stratified analyses were performed on each interaction. These results

Table 19-22.
Analysis of Lupus Panel: Antinuclear Antibody (ANA)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***936***	***13.7***	***0.81 (0.64,1.03)***	***0.092***
	Comparison	***1,264***	***16.4***		
Officer	Ranch Hand	363	15.7	0.86 (0.59,1.23)	0.454
	Comparison	492	17.9		
Enlisted Flyer	Ranch Hand	160	16.3	0.98 (0.56,1.72)	0.999
	Comparison	200	16.5		
Enlisted Groundcrew	Ranch Hand	413	10.9	0.69 (0.47,1.02)	0.073
	Comparison	572	15.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***0.80 (0.63,1.02)***	***0.067***	AGE ($p < 0.001$)
Officer	0.84 (0.59,1.22)	0.365	
Enlisted Flyer	0.97 (0.55,1.71)	0.921	
Enlisted Groundcrew	0.69 (0.47,1.01)	0.058	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-22. (Continued)
Analysis of Lupus Panel: Antinuclear Antibody (ANA)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	16.4	0.95 (0.77,1.16)	0.599
Medium	172	10.5		
High	168	12.5		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
498	1.02 (0.82,1.27)	0.865	AGE (p=0.005) RACE (p=0.149) DRKYR (p=0.002)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-22. (Continued)
Analysis of Lupus Panel: Antinuclear Antibody (ANA)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	17.1		
Background RH	367	15.5	0.88 (0.63,1.22)	0.445
Low RH	256	14.8	0.84 (0.58,1.23)	0.378
High RH	255	11.4	0.63 (0.41,0.96)	0.030
Low plus High RH	511	13.1	0.73 (0.54,1.00)	0.047

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,033			DXCAT*DRKYR (p=0.002) AGE (p<0.001)
Background RH	361	****	****	
Low RH	250	****	****	
High RH	248	****	****	
Low plus High RH	498	****	****	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Categorized dioxin-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-18 for further analysis of this interaction.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-22. (Continued)
Analysis of Lupus Panel: Antinuclear Antibody (ANA)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	16.6 (289)	14.9 (295)	10.9 (294)	0.90 (0.79,1.03)	0.137
5	15.3 (294)	16.1 (292)	11.0 (292)	0.93 (0.84,1.04)	0.233
6[c]	15.4 (293)	16.1 (292)	11.0 (292)	0.90 (0.80,1.02)	0.099

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	859	0.95 (0.82,1.09)**	0.431**	CURR*RACE (p=0.023) CURR*DRKYR (p=0.002) AGE (p<0.001)
5	859	0.97 (0.86,1.09)**	0.554**	CURR*RACE (p=0.014) CURR*DRKYR (p=0.003) AGE (p<0.001)
6[d]	858	0.94 (0.83,1.07)**	0.341**	CURR*RACE (p=0.016) CURR*DRKYR (p=0.003) AGE (p<0.001)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interactions ($p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-18 for further analysis of these interactions.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-23.
Analysis of Lupus Panel: Thyroid Microsomal Antibody

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***936***	***4.4***	***1.61 (1.02,2.55)***	***0.054***
	Comparison	***1,264***	***2.8***		
Officer	Ranch Hand	363	4.1	1.20 (0.59,2.45)	0.739
	Comparison	492	3.5		
Enlisted Flyer	Ranch Hand	160	5.0	3.46 (0.90,13.25)	0.108
	Comparison	200	1.5		
Enlisted Groundcrew	Ranch Hand	413	4.4	1.69 (0.84,3.40)	0.189
	Comparison	572	2.6		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	****	****	GROUP*CSMOK (p=0.001) GROUP*ALC (p=0.002) GROUP*DRKYR (p<0.001) PHYACT (p=0.088)
Officer	****	****	
Enlisted Flyer	****	****	
Enlisted Groundcrew	****	****	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

**** Group-by-covariate interactions ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-19 for further analysis of these interactions.

Table 19-23. (Continued)
Analysis of Lupus Panel: Thyroid Microsomal Antibody

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	6.4	0.91 (0.67,1.24)	0.559
Medium	172	4.1		
High	168	5.4		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
498	0.82 (0.59,1.14)**	0.228**	INIT*DRKYR (p=0.014) INIT*CSMOK (p=0.025) PACKYR (p=0.031) ALC (p<0.001) PHYACT (P=0.034)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interactions ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-19 for further analysis of these interactions.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-23. (Continued)
Analysis of Lupus Panel: Thyroid Microsomal Antibody

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	2.8		
Background RH	367	3.5	1.31 (0.67,2.56)	0.431
Low RH	256	5.9	2.14 (1.13,4.07)	0.020
High RH	255	4.7	1.74 (0.87,3.47)	0.119
Low plus High RH	511	5.3	1.94 (1.13,3.33)	0.016

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,033			DXCAT*CSMOK (p=0.001) DXCAT*ALC (p<0.001) DXCAT*DRKYR (p<0.001) AGE (p=0.120)
Background RH	361	****	****	
Low RH	250	****	****	
High RH	248	****	****	
Low plus High RH	498	****	****	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

**** Categorized dioxin-by-covariate interactions ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented; refer to Appendix Table O-2-19 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-23. (Continued)
Analysis of Lupus Panel: Thyroid Microsomal Antibody

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	3.5 (289)	5.8 (295)	4.4 (294)	1.08 (0.87,1.34)	0.478
5	3.1 (294)	5.8 (292)	4.8 (292)	1.10 (0.91,1.32)	0.327
6[c]	3.1 (293)	5.8 (292)	4.8 (292)	1.06 (0.86,1.29)	0.587

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	868	1.09 (0.88,1.34)**	0.449**	CURR*ALC (p=0.044) PACKYR (p=0.009)
5	868	1.10 (0.92,1.32)	0.302	PACKYR (p=0.009) ALC (p=0.014)
6[d]	867	1.07 (0.88,1.30)	0.507	PACKYR (p=0.013) ALC (p=0.014)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-19 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

are displayed in Appendix Table O-2-19. Ranch Hands with more than 40 drink-years had significantly higher percentage of thyroid microsomal antibody than Comparisons overall and in each of the occupational categories.

The unadjusted analysis of Model 2 did not reveal a significant association between the thyroid microsomal antibody and initial dioxin (Table 19-23(c): $p=0.559$). The adjusted analysis revealed significant initial dioxin-by-lifetime alcohol history and initial dioxin-by-current cigarette smoking interactions (Table 19-23(d): $p=0.014$ and $p=0.025$). Lifetime cigarette smoking history, current alcohol use, and the physical activity index also were significant in the final adjusted model. Removal of the interactions did not reveal a significant association between initial dioxin and the presence of the thyroid microsomal antibodies ($p=0.228$). Stratified results of each interaction are presented in Appendix Table O-2-19.

In Model 3, the unadjusted analysis exhibited a significantly higher percentage of positive thyroid microsomal antibody test results in the low Ranch Hand category (5.9%) and the low plus high Ranch Hand category (5.3%) than in the Comparison group (2.8%) (Table 19-23(e): $p=0.020$, Est. RR=2.14 and $p=0.016$, Est. RR=1.94 respectively). Adjusting for covariates in Model 3 revealed three highly significant interactions with categorized dioxin: categorized dioxin-by-current cigarette smoking, categorized dioxin-by-current alcohol use, and categorized dioxin-by-lifetime alcohol history (Table 19-23(f): $p=0.001$, $p<0.001$, and $p<0.001$ respectively). Age also was retained in the final adjusted model. Stratified results of each interaction are shown in Appendix Table O-2-19. Ranch Hands who were current or former smokers, light current drinkers (0-1 drink/day), and heavy lifetime drinkers (>40 drink-years) had higher percentages of thyroid microsomal antibodies present than Comparisons.

The unadjusted analyses of Models 4 through 6 did not show any significant relationships between current dioxin and thyroid microsomal antibodies (Table 19-23(g): $p>0.32$ for unadjusted analyses). Adjusting for covariates in Model 4 revealed a significant current dioxin-by-current alcohol use interaction (Table 19-23(h): $p=0.044$). Lifetime smoking history also was significant in the final adjusted model. Removal of the interaction did not reveal a significant association between current dioxin and the presence of thyroid microsomal antibodies. Stratified results of the interaction in Model 4 are presented in Appendix Table O-2-19. The adjusted analyses of Model 5 and 6 did not display any significant results (Table 19-23(h): $p>0.30$ for adjusted analyses).

Lupus Panel: MSK Smooth Muscle Antibody

The analysis of mouse stomach kidney (MSK) smooth muscle antibody in Model 1 did not show any significant results (Table 19-24(a,b): $p>0.31$ for unadjusted and adjusted analyses). Age, race, and occupation were accounted for in the final adjusted model.

In Model 2, the unadjusted and adjusted analyses revealed significant inverse relationships between MSK smooth muscle antibodies and initial dioxin (Table 19-24(c,d): $p=0.035$, Est. RR=0.60 and $p=0.022$, Adj. RR=0.57). The percentage of participants testing positive for the smooth muscle antibody in the low, medium, and high initial dioxin

Table 19-24.
Analysis of Lupus Panel: MSK Smooth Muscle Antibody

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Percent Present	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***936***	***3.0***	***0.94 (0.58,1.54)***	***0.914***
	Comparison	***1,264***	***3.2***		
Officer	Ranch Hand	363	4.7	1.29 (0.66,2.55)	0.567
	Comparison	492	3.7		
Enlisted Flyer	Ranch Hand	160	1.9	0.75 (0.18,3.17)	0.968
	Comparison	200	2.5		
Enlisted Groundcrew	Ranch Hand	413	1.9	0.65 (0.28,1.51)	0.416
	Comparison	572	3.0		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	***0.94 (0.58,1.54)***	***0.805***	AGE (p=0.139) RACE (p=0.060) OCC (p=0.150)
Officer	1.28 (0.65,2.51)	0.481	
Enlisted Flyer	0.75 (0.18,3.20)	0.700	
Enlisted Groundcrew	0.64 (0.28,1.51)	0.312	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-24.
Analysis of Lupus Panel: MSK Smooth Muscle Antibody

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	3.5	0.60 (0.36,1.00)	0.035
Medium	172	3.5		
High	168	1.2		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
	Analysis Results for Log_2 (Initial Dioxin)[c]		
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
511	0.57 (0.33,0.97)	0.022	PHYACT (p=0.015)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-24. (Continued)
Analysis of Lupus Panel: MSK Smooth Muscle Antibody

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	3.1		
Background RH	367	3.8	1.32 (0.69,2.51)	0.405
Low RH	256	4.3	1.37 (0.68,2.75)	0.383
High RH	255	1.2	0.34 (0.10,1.11)	0.073
Low plus High RH	511	2.7	0.83 (0.44,1.57)	0.563

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,051			AGE (p=0.048) RACE (p=0.140)
Background RH	367	1.27 (0.67,2.43)	0.467	
Low RH	256	1.27 (0.63,2.58)	0.503	
High RH	255	0.37 (0.11,1.23)	0.105	
Low plus High RH	511	0.84 (0.44,1.60)	0.594	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-24. (Continued)
Analysis of Lupus Panel: MSK Smooth Muscle Antibody

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	3.8 (289)	4.1 (295)	1.7 (294)	0.78 (0.59,1.03)	0.070
5	3.7 (294)	3.8 (292)	2.1 (292)	0.85 (0.68,1.05)	0.143
6[c]	3.8 (293)	3.8 (292)	2.1 (292)	0.81 (0.64,1.02)	0.082

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	878	0.80 (0.60,1.07)	0.131	AGE (p=0.097)
5	878	0.87 (0.69,1.09)	0.232	AGE (p=0.081)
6[d]	877	0.83 (0.65,1.06)	0.151	AGE (p=0.096)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

categories were 3.5 percent, 3.5 percent, and 1.2 percent. The physical activity index was significant in the final adjusted model.

The unadjusted analysis of Model 3 revealed that the percentage of participants testing positive was marginally significantly lower for MSK smooth muscle antibodies in the high Ranch Hand category (1.2%) than in the Comparison group (3.1%) (Table 19-24(e): $p=0.073$, Est. RR=0.34). The results of the adjusted Model 3 analysis were nonsignificant. Age and race were covariates included in the final adjusted model.

The unadjusted analyses of Models 4 and 6 displayed marginally significant inverse associations between the smooth muscle antibody and current dioxin (Table 19-24(g): $p=0.070$, Est. RR=0.78; $p=0.082$, Est. RR=0.81). The percentage of participants testing positive for the smooth muscle antibody in the low, medium, and high categories were 3.8, 4.1, and 1.7 percent for Model 4 and 3.8, 3.8, and 2.1 percent for Model 6. The unadjusted analysis of Model 5 was nonsignificant ($p=0.143$). The adjusted analyses of Models 4 through 6 did not reveal any significant associations between current dioxin and smooth muscle antibody (Table 19-24(h): $p>0.13$ for adjusted analyses). Age was retained in each of the final adjusted models for Models 4 through 6.

Lupus Panel: MSK Mitochondrial Antibody

Due to a sparse number of abnormal findings, the adjusted analyses for Models 1 through 6 were not performed.

The unadjusted Model 1 analysis did not reveal any significant differences between Ranch Hands and Comparisons in the presence of MSK mitochondrial antibodies (Table 19-25(a): $p>0.62$). Because only one Ranch Hand (in the low initial dioxin category) had an MSK mitochondrial antibody present, no unadjusted Model 2 analysis was performed. The unadjusted analyses of Models 3 through 6 did not exhibit any significant associations between the presence of MSK mitochondrial antibodies and categorized dioxin or current dioxin (Table 19-25(e,g): $p>0.11$ for all analyses).

Lupus Panel: MSK Parietal Antibody

The unadjusted analysis of the parietal antibody did not detect a significant difference between Ranch Hands and Comparisons in Model 1 (Table 19-26(a): $p>0.26$ for unadjusted analysis). The adjusted analysis of Model 1 revealed a significant group-by-race interaction (Table 19-26(b): $p=0.014$). Age, current cigarette smoking, and current alcohol use also were included in the final adjusted model. Removal of the group-by-race interaction in Model 1 revealed a marginally significant difference between Ranch Hands and Comparisons within the officer category (Table 19-26(b): $p=0.084$, Est. RR=1.87). Stratified analyses of the interaction are shown in Appendix Table O-2-20.

Models 2 and 3 did not reveal any significant associations between initial dioxin and the parietal antibody test in the unadjusted and adjusted analyses (Table 19-26(c-f): $p>0.22$). No covariates were significant in the Model 2 adjusted analysis. Age, current cigarette smoking, and current alcohol use were retained in the final adjusted model for Model 3.

Table 19-25.
Analysis of MSK Mitochondrial Antibody

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***936***	***0.2***	***0.90 (0.15,5.40)***	***0.999***
	Comparison	***1,264***	***0.2***		
Officer	Ranch Hand	363	0.6	2.72 (0.25,30.12)	0.791
	Comparison	493	0.2		
Enlisted Flyer	Ranch Hand	160	0.0	--	--
	Comparison	200	0.0		
Enlisted Groundcrew	Ranch Hand	413	0.0	0.28 (0.01,5.76)	0.627
	Comparison	572	0.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks**
All	--	--	
Officer	--	--	
Enlisted Flyer	--	--	
Enlisted Groundcrew	--	--	

--: Adjusted analysis not performed due to the sparse number of abnormalities.

Table 19-25. (Continued)
Analysis of MSK Mitochondrial Antibody

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	0.6	--	--
Medium	172	0.0		
High	168	0.0		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)			
n	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
--	--	--	

[a] Adjusted for percent body fat at the time of duty and change in percent body fat from the time of duty to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

--: Adjusted analysis not performed due to the sparse number of abnormalities.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-25. (Continued)
Analysis of MSK Mitochondrial Antibody

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED

Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	0.3		
Background RH	367	0.3	1.41 (0.14,14.30)	0.770
Low RH	256	0.4	1.04 (0.10,10.50)	0.971
High RH	255	0.0	--	--
Low plus High RH	511	0.2	0.49 (0.05,5.04)	0.545

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED

Dioxin Category	n	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Comparison	--			
Background RH	--	--	--	
Low RH	--	--	--	
High RH	--	--	--	
Low plus High RH	--	--	--	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty and change in percent body fat from the time of duty to the date of the blood draw for dioxin.

--: Adjusted analysis not performed due to the sparse number of abnormalities.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-25. (Continued)
Analysis of MSK Mitochondrial Antibody

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	0.3 (289)	0.3 (295)	0.0 (294)	0.44 (0.15,1.26)	0.126
5	0.7 (294)	0.0 (292)	0.0 (292)	0.58 (0.32,1.04)	0.114
6[c]	0.7 (293)	0.0 (292)	0.0 (292)	0.63 (0.31,1.26)	0.243

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	--	--	--	
5	--	--	--	
6[c]	--	--	--	

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

--: Adjusted analysis not performed due to the sparse number of abnormalities.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-26.
Analysis of Lupus Panel: MSK Parietal Antibody

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	Group	n	Percent Present	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***936***	***2.4***	***0.90 (0.52,1.55)***	***0.804***
	Comparison	***1,264***	***2.6***		
Officer	Ranch Hand	363	3.0	1.51 (0.63,3.59)	0.479
	Comparison	492	2.0		
Enlisted Flyer	Ranch Hand	160	1.9	0.94 (0.21,4.25)	0.999
	Comparison	200	2.0		
Enlisted Groundcrew	Ranch Hand	413	1.9	0.58 (0.25,1.33)	0.265
	Comparison	572	3.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks[a]
All	***0.87 (0.50,1.51)****	***0.618****	GROUP*RACE (p=0.014)
Officer	1.87 (0.92,3.80)**	0.084**	AGE (p=0.105)
Enlisted Flyer	1.14 (0.36,3.62)**	0.828**	CSMOK (p=0.085)
Enlisted Groundcrew	1.18 (0.57,2.46)**	0.659**	ALC (p=0.031)

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

** Group-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-20 for further analysis of this interaction.

Table 19-26. (Continued)
Analysis of Lupus Panel: MSK Parietal Antibody

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	3.5	0.88 (0.59,1.33)	0.533
Medium	172	2.9		
High	168	1.8		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[a]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
511	0.88 (0.59,1.33)	0.533	

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-26. (Continued)
Analysis of Lupus Panel: MSK Parietal Antibody

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	2.4		
Background RH	367	1.4	0.60 (0.23,1.60)	0.312
Low RH	256	3.1	1.29 (0.57,2.91)	0.537
High RH	255	2.4	0.94 (0.38,2.33)	0.891
Low plus High RH	511	2.7	1.11 (0.57,2.17)	0.753

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,035			AGE (p=0.027) CSMOK (p=0.073) ALC (p=0.064)
Background RH	365	0.55 (0.21,1.45)	0.226	
Low RH	253	1.21 (0.54,2.74)	0.643	
High RH	251	1.01 (0.40,2.51)	0.989	
Low plus High RH	504	1.12 (0.57,2.18)	0.750	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-26. (Continued)
Analysis of Lupus Panel: MSK Parietal Antibody

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	0.7 (289)	3.7 (295)	2.0 (294)	1.17 (0.87,1.57)	0.319
5	0.3 (294)	4.1 (292)	2.1 (292)	1.16 (0.89,1.51)	0.279
6[c]	0.3 (293)	4.1 (292)	2.1 (292)	1.16 (0.87,1.55)	0.307

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	878	1.29 (0.94,1.77)	0.118	AGE (p=0.012) CSMOK (p=0.072)
5	878	1.25 (0.95,1.66)	0.114	AGE (p=0.013) CSMOK (p=0.075)
6[d]	877	1.29 (0.95,1.76)	0.104	AGE (p=0.011) CSMOK (p=0.069)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

The unadjusted and adjusted analysis in Models 4 through 6 did not reveal any significant associations between current dioxin and the existence of parietal cell antibodies (Table 19-26(g,h): $p>0.10$). The covariates age and current cigarette smoking were included in each of the final models for Models 4, 5, and 6.

Lupus Panel: Rheumatoid Factor

The unadjusted Model 1 analysis of rheumatoid factor disclosed no significant differences between Ranch Hands and Comparisons (Table 19-27(a): $p>0.11$ for all contrasts). In the adjusted analysis, the relative risk was marginally significant for officers (Table 19-27(b): $p=0.082$, Adj. RR=0.72), but was nonsignificant for all other occupational categories ($p>0.37$).

A significant negative association between initial dioxin and rheumatoid factor was revealed in the unadjusted Model 2 analysis (Table 19-27(c): $p=0.028$, Est. RR=0.80). The percentage of Ranch Hands with the lupus panel rheumatoid factor present were 18.1, 12.2, and 13.1 percent for the low, medium, and high initial dioxin categories. In the adjusted analysis, initial dioxin-by-age and initial dioxin-by-occupation interactions were significant (Table 19-27(d): $p=0.007$ and $p=0.037$). Stratified results are presented in Appendix Table O-2-21. After removing the interactions from the model, the adjusted relative risk was marginally significant ($p=0.058$, Adj. RR=0.80).

In the unadjusted Model 3 analysis, the difference in the percentage of participants with a positive rheumatoid factor between the high Ranch Hand category (10.6%) and the Comparison category (16.8%) was significant (Table 19-27(e): $p=0.012$, Est. RR=0.57). All other contrasts were nonsignificant ($p>0.21$). In the adjusted analysis, the categorized dioxin-by-occupation and categorized dioxin-by-physical activity index interactions were significant (Table 19-27(f): $p=0.004$ and $p=0.019$). Stratified results are presented in Appendix Table O-2-21. After removing the interactions from the model, the high Ranch Hand versus Comparison contrast remained significant ($p=0.035$, Adj. RR=0.62) and the other contrasts remained nonsignificant ($p>0.31$). Age and current alcohol use were covariates retained in the final adjusted model.

The inverse association between current dioxin and a positive rheumatoid factor was significant in the unadjusted and adjusted analyses of Models 4 and 5 (Table 19-27(g,h): $p=0.038$, Est. RR=0.87 and $p=0.023$, Est. RR=0.88 for the unadjusted analyses of Models 4 and 5; $p=0.013$, Adj. RR=0.83 and $p=0.008$, Adj. RR=0.85 for the adjusted analyses of Models 4 and 5). The adjusted analysis of Model 6 was marginally significant (Table 19-27(h): $p=0.053$, Adj. RR=0.88). However, when occupation was removed from Model 4, the association became marginally significant (Table O-13-17(c): $p=0.072$, Adj. RR=0.88). The association became nonsignificant (Appendix Table O-3-17: $p=0.207$) in Model 6 after removing occupation from the final model. Models 4, 5, and 6 each were adjusted for age, occupation, and the physical activity index.

Table 19-27.
Analysis of Lupus Panel: Rheumatoid Factor

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***936***	***15.2***	***0.89 (0.71,1.13)***	***0.367***
	Comparison	***1,264***	***16.7***		
Officer	Ranch Hand	363	15.2	0.74 (0.51,1.06)	0.118
	Comparison	492	19.5		
Enlisted Flyer	Ranch Hand	160	13.8	0.78 (0.44,1.39)	0.484
	Comparison	200	17.0		
Enlisted Groundcrew	Ranch Hand	413	15.7	1.13 (0.80,1.61)	0.551
	Comparison	572	14.2		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***0.90 (0.71,1.14)***	***0.371***	AGE (p=0.005) ALC (p=0.097)
Officer	0.72 (0.50,1.04)	0.082	
Enlisted Flyer	0.81 (0.45,1.45)	0.472	
Enlisted Groundcrew	1.16 (0.81,1.67)	0.405	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-27. (Continued)
Analysis of Lupus Panel: Rheumatoid Factor

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	18.1	0.80 (0.65,0.98)	0.028
Medium	172	12.2		
High	168	13.1		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
	Analysis Results for Log_2 (Initial Dioxin)[c]		
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
511	0.80 (0.64,1.01)**	0.058**	INIT*OCC (p=0.007) INIT*AGE (p=0.037)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Log_2 (initial dioxin)-by-covariate interactions ($p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-21 for further analysis of these interactions.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-27. (Continued)
Analysis of Lupus Panel: Rheumatoid Factor

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	16.8		
Background RH	367	16.1	0.96 (0.70,1.33)	0.823
Low RH	256	18.4	1.11 (0.78,1.58)	0.575
High RH	255	10.6	0.57 (0.37,0.88)	0.012
Low plus High RH	511	14.5	0.83 (0.62,1.11)	0.211

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,035			DXCAT*OCC (p=0.004) DXCAT*PHYACT (p=0.019) AGE (p=0.084) ALC (p=0.093)
Background RH	365	0.95 (0.68,1.32)**	0.744**	
Low RH	253	1.08 (0.75,1.55)**	0.670**	
High RH	251	0.62 (0.40,0.97)**	0.035**	
Low plus High RH	504	0.86 (0.63,1.16)**	0.312**	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

** Categorized dioxin-by-covariate interactions ($p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of these interactions; refer to Appendix Table O-2-21 for further analysis of these interactions.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-27. (Continued)
Analysis of Lupus Panel: Rheumatoid Factor

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Present/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	16.6 (289)	17.6 (295)	11.2 (294)	0.87 (0.76,0.99)	0.038
5	18.0 (294)	17.1 (292)	10.3 (292)	0.88 (0.79,0.98)	0.023
6[c]	18.1 (293)	17.1 (292)	10.3 (292)	0.91 (0.81,1.03)	0.126

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	878	0.83 (0.72,0.96)	0.013	AGE (p=0.094) OCC (p=0.070) PHYACT (p=0.070)
5	878	0.85 (0.75,0.96)	0.008	AGE (p=0.084) OCC (p=0.068) PHYACT (p=0.071)
6[d]	877	0.88 (0.77,1.00)	0.053	AGE (p=0.056) OCC (p=0.074) PHYACT (p=0.067)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

In the unadjusted and adjusted Model 1 analyses of B cell clones detected by serum protein electrophoresis, no significant differences between Ranch Hands and Comparisons were found (Table 19-28(a,b): $p \geq 0.12$ for all contrasts). Age was the only significant covariate in the adjusted model.

The association between initial dioxin and B cell clones detected by serum protein electrophoresis was nonsignificant in the unadjusted and adjusted Model 2 analyses (Table 19-28(c,d): $p=0.838$ and $p=0.325$). Age and the physical activity index were included in the final adjusted model.

In the unadjusted Model 3 analyses of B cell clones detected by serum protein electrophoresis, the contrast between the background Ranch Hand and the Comparison categories was marginally significant (Table 19-28(e): $p=0.072$, Est. RR=1.97). The remaining unadjusted contrasts and all of the adjusted contrasts were nonsignificant (Table 19-28(e,f): $p>0.13$). In the final adjusted model, age and occupation were retained.

The association between current dioxin and B cell clones detected by serum protein electrophoresis was nonsignificant in the unadjusted and adjusted analyses of Models 4, 5, and 6 (Table 19-28(g,h): $p>0.14$ for all analyses). The current dioxin-by-current alcohol use interaction was significant in Models 5 and 6 (Table 19-28(h): $p=0.030$ and $p=0.037$). Stratified results for these interactions are presented in Appendix Table O-2-22. Age also was significant in all three adjusted models.

Lupus Panel: Other Antibodies (ANA and MSK)

Unadjusted and adjusted results from the Model 1, 2, and 3 analyses of other antibodies (ANA and MSK) were nonsignificant (Table 19-29(a-f): $p \geq 0.15$ for all analyses). Race was included in each of the adjusted models. The physical activity index also was retained in Models 1 and 3.

In Models 4, 5, and 6, the unadjusted analyses of other antibodies (ANA and MSK) showed no significant association with current dioxin (Table 19-29(g): $p>0.42$ for all models). The adjusted analyses of Models 4 and 5 retained no significant covariates; therefore, the results are identical to the unadjusted results. In the adjusted analysis of Model 6, the current dioxin-by-race interaction was significant (Table 19-29(h): $p=0.046$). Results for each race stratum are presented in Appendix Table O-2-23. After removing the current dioxin-by-race interaction from the final model, the association between current dioxin and other antibodies (ANA and MSK) was nonsignificant ($p=0.417$).

Table 19-28.
Analysis of Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***936***	***2.4***	***1.36 (0.75,2.47)***	***0.392***
	Comparison	***1,264***	***1.7***		
Officer	Ranch Hand	363	3.3	2.07 (0.84,5.11)	0.168
	Comparison	492	1.6		
Enlisted Flyer	Ranch Hand	160	3.8	1.26 (0.40,3.98)	0.922
	Comparison	200	3.0		
Enlisted Groundcrew	Ranch Hand	413	1.0	0.69 (0.21,2.31)	0.754
	Comparison	572	1.4		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***1.35 (0.74,2.45)***	***0.328***	AGE (p=0.010)
Officer	2.05 (0.83,5.08)	0.120	
Enlisted Flyer	1.25 (0.39,3.95)	0.706	
Enlisted Groundcrew	0.69 90.21,2.30)	0.546	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-28. (Continued)
Analysis of Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	171	1.2	1.05 (0.66,1.68)	0.838
Medium	172	2.9		
High	168	1.8		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
511	1.30 (0.78,2.17)	0.325	AGE ($p<0.001$) PHYACT ($p=0.102$)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-28. (Continued)
Analysis of Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,051	1.9		
Background RH	367	3.3	1.97 (0.94,4.12)	0.072
Low RH	256	1.6	0.77 (0.26,2.29)	0.640
High RH	255	2.4	1.13 (0.45,2.88)	0.789
Low plus High RH	511	2.0	0.95 (0.44,2.07)	0.906

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,051			AGE (p=0.045) OCC (p=0.071)
Background RH	367	1.79 (0.84,3.83)	0.134	
Low RH	256	0.70 (0.23,2.07)	0.514	
High RH	255	1.36 (0.51,3.64)	0.534	
Low plus High RH	511	0.97 (0.44,2.13)	0.943	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-28. (Continued)
Analysis of Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[a]	Current Dioxin Category Percent Present/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) Est. Relative Risk (95% C.I.)[b]	p-Value
4	2.4 (289)	3.1 (295)	2.0 (294)	0.85 (0.63,1.16)	0.297
5	2.7 (294)	3.1 (292)	1.7 (292)	0.88 (0.69,1.12)	0.306
6[c]	2.7 (293)	3.1 (292)	1.7 (292)	0.82 (0.63,1.07)	0.147

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[a]	n	Analysis Results for Log_2 (Current Dioxin + 1) Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	878	0.91 (0.66,1.27)	0.572	AGE (p=0.006)
5	869	0.92 (0.71,1.20)**	0.543**	CURR*ALC (p=0.030) AGE (p=0.005)
6[d]	868	0.87 (0.65,1.16)**	0.340**	CURR*ALC (p=0.037) AGE (p=0.006)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this Interaction; refer to Appendix Table O-2-22 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-29.
Analysis of Lupus Panel: Other Antibodies (ANA and MSK)

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Present**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***932***	***3.1***	***0.76 (0.48,1.21)***	***0.300***
	Comparison	***1,261***	***4.0***		
Officer	Ranch Hand	362	3.0	0.64 (0.31,1.32)	0.297
	Comparison	490	4.7		
Enlisted Flyer	Ranch Hand	159	4.4	0.88 (0.33,2.35)	0.988
	Comparison	200	5.0		
Enlisted Groundcrew	Ranch Hand	411	2.7	0.85 (0.40,1.81)	0.808
	Comparison	571	3.2		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***0.76 (0.48,1.21)***	***0.246***	RACE (p=0.032) PHYACT (p=0.042)
Officer	0.64 (0.31,1.33)	0.228	
Enlisted Flyer	0.89 (0.33,2.40)	0.814	
Enlisted Groundcrew	0.84 (0.39,1.80)	0.653	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-29. (Continued)
Analysis of Lupus Panel: Other Antibodies (ANA and MSK)

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Percent Present	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	170	1.2	1.15 (0.77,1.71)	0.508
Medium	172	4.7		
High	167	3.0		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
Analysis Results for Log_2 (Initial Dioxin)[c]			
n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
509	1.12 (0.76,1.67)	0.569	RACE (p=0.137)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-29. (Continued)
Analysis of Lupus Panel: Other Antibodies (ANA and MSK)

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Present	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,048	4.3		
Background RH	365	3.3	0.77 (0.40,1.49)	0.444
Low RH	255	2.4	0.53 (0.22,1.26)	0.150
High RH	254	3.5	0.81 (0.39,1.68)	0.566
Low plus High RH	509	2.9	0.67 (0.37,1.21)	0.184

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,046			RACE (p=0.080) PHYACT (p=0.051)
Background RH	365	0.77 (0.40,1.49)	0.438	
Low RH	255	0.54 (0.23,1.29)	0.168	
High RH	254	0.78 (0.38,1.63)	0.510	
Low plus High RH	509	0.66 (0.37,1.21)	0.180	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-29. (Continued)
Analysis of Lupus Panel: Other Antibodies (ANA and MSK)

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED

Model[a]	Current Dioxin Category Percent Present/(n) Low	Medium	High	Analysis Results for Log_2 (Current Dioxin + 1) Est. Relative Risk (95% C.I.)[b]	p-Value
4	3.1 (287)	2.7 (294)	3.4 (293)	1.07 (0.83,1.39)	0.595
5	3.4 (292)	2.7 (291)	3.1 (291)	1.05 (0.83,1.31)	0.697
6[c]	3.4 (291)	2.8 (291)	3.1 (291)	1.10 (0.87,1.41)	0.424

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED

Model[a]	Analysis Results for Log_2 (Current Dioxin + 1) n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	874	1.07 (0.83,1.39)	0.595	
5	874	1.05 (0.83,1.31)	0.697	
6[d]	873	1.11 (0.87,1.41)**	0.417**	CURR*RACE (p=0.046)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

** Log_2 (current dioxin + 1)-by-covariate interaction ($0.01 < p \leq 0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction; refer to Appendix Table O-2-23 for further analysis of this interaction.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Lupus Panel: Summary Index

The unadjusted and adjusted Model 1 analyses of the lupus panel summary index showed no significant differences between Ranch Hands and Comparisons (Table 19-30(a,b): $p>0.12$ for all contrasts). Age and race were significant covariates in the adjusted analysis.

A marginally significant negative association between the lupus panel summary index and initial dioxin was discovered in the unadjusted analysis of Model 2 (Table 19-30(c): $p=0.067$, Est. RR=0.88). However, the association became nonsignificant after adjusting for age and current alcohol use (Table 19-30(d): $p=0.658$).

In the unadjusted Model 3 analysis of the lupus panel summary index, the contrasts between the high Ranch Hand category and Comparisons and between the low plus high Ranch Hand category and Comparisons were significant (Table 19-30(e): $p=0.002$, Est. RR=0.62 for high Ranch Hands vs. Comparisons; $p=0.021$, Est. RR=0.77 for low plus high Ranch Hands vs. Comparisons). The percentage of participants with abnormal lupus panel index results were 41.4 percent for Comparisons, 31.1 percent in the high Ranch Hand category, and 35.8 percent in the low plus high Ranch Hand category. The contrasts of the background Ranch Hand and low Ranch Hand categories versus Comparisons were nonsignificant ($p>0.68$). In the adjusted analysis, the high Ranch Hand versus Comparison and the low plus high Ranch Hand versus Comparison contrasts remained significant (Table 19-30(f): $p=0.019$, Adj. RR=0.70 for high Ranch Hands vs. Comparisons; $p=0.040$, Adj. RR=0.79 for low plus high Ranch Hands vs. Comparisons). The background Ranch Hand and low Ranch Hand contrasts remained nonsignificant ($p>0.39$). Age, race, and current cigarette smoking were included in the final adjusted model.

A significant negative association between current dioxin and the lupus panel summary index was detected in the unadjusted analyses of Models 4, 5, and 6 (Table 19-30(g): $p=0.028$, Est. RR=0.90 for Model 4; $p=0.042$, Est. RR=0.92 for Model 5; $p=0.030$, Est. RR=0.91 for Model 6). However, after adjusting each model for age and lifetime cigarette smoking history, the associations became nonsignificant (Table 19-30(h): $p=0.248$ for Model 4; $p=0.259$ for Model 5; and $p=0.294$ for Model 6).

Longitudinal Analysis

Longitudinal analyses for the CD4-CD8 ratio examined the paired difference between the measurements from 1985 and 1992. These paired differences measured the change in the ratio over time. Each of the three models used in the longitudinal analysis were adjusted for age and the CD4-CD8 ratio measured in 1985. The analyses of Models 2 and 3 also were adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

CD4-CD8 Ratio

Results from the Model 1 and Model 2 longitudinal analyses of the ratio of CD4 to CD8 were nonsignificant (Table 19-31(a,b): $p>0.10$ for all analyses).

Table 19-30.
Analysis of Lupus Panel: Summary Index

a) MODEL 1: RANCH HANDS VS. COMPARISONS — UNADJUSTED					
Occupational Category	**Group**	**n**	**Percent Abnormal**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***933***	***37.1***	***0.88 (0.74,1.05)***	***0.170***
	Comparison	***1,263***	***40.1***		
Officer	Ranch Hand	363	41.0	0.90 (0.68,1.18)	0.481
	Comparison	492	43.7		
Enlisted Flyer	Ranch Hand	159	38.4	0.97 (0.64,1.49)	0.989
	Comparison	200	39.0		
Enlisted Groundcrew	Ranch Hand	411	33.1	0.83 (0.64,1.09)	0.196
	Comparison	571	37.3		

b) MODEL 1: RANCH HANDS VS. COMPARISONS — ADJUSTED			
Occupational Category	**Adj. Relative Risk (95% C.I.)**	**p-Value**	**Covariate Remarks[a]**
All	***0.87 (0.73,1.04)***	***0.124***	AGE ($p<0.001$) RACE ($p=0.042$)
Officer	0.88 (0.67,1.16)	0.368	
Enlisted Flyer	0.97 (0.63,1.49)	0.875	
Enlisted Groundcrew	0.83 (0.63,1.09)	0.179	

[a] Covariates and associated p-values correspond to final model based on all participants with available data.

Table 19-30. (Continued)
Analysis of Lupus Panel: Summary Index

c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED				
Initial Dioxin Category Summary Statistics			**Analysis Results for Log_2 (Initial Dioxin)[a]**	
Initial Dioxin	**n**	**Percent Abnormal**	**Estimated Relative Risk (95% C.I.)[b]**	**p-Value**
Low	170	40.6	0.88 (0.76,1.01)	0.067
Medium	172	33.7		
High	167	32.9		

d) MODEL 2: RANCH HANDS — INITIAL DIOXIN — ADJUSTED			
	Analysis Results for Log_2 (Initial Dioxin)[c]		
n	**Adj. Relative Risk (95% C.I.)[b]**	**p-Value**	**Covariate Remarks**
502	0.97 (0.83,1.13)	0.658	AGE ($p<0.001$) ALC ($p=0.123$)

[a] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[b] Relative risk for a twofold increase in initial dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.

Table 19-30. (Continued)
Analysis of Lupus Panel: Summary Index

e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED				
Dioxin Category	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,050	41.4		
Background RH	366	39.6	0.96 (0.75,1.22)	0.720
Low RH	255	40.4	0.94 (0.71,1.25)	0.685
High RH	254	31.1	0.62 (0.46,0.84)	0.002
Low plus High RH	509	35.8	0.77 (0.62,0.96)	0.021

f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — ADJUSTED				
Dioxin Category	n	Adj. Relative Risk (95% C.I.)[ac]	p-Value	Covariate Remarks
Comparison	1,048			AGE ($p<0.001$) RACE ($p=0.081$) CSMOK ($p=0.101$)
Background RH	366	0.90 (0.70,1.15)	0.397	
Low RH	255	0.89 (0.67,1.18)	0.408	
High RH	254	0.70 (0.52,0.94)	0.019	
Low plus High RH	509	0.79 (0.63,0.99)	0.040	

[a] Relative risk and confidence interval relative to Comparisons.

[b] Adjusted for percent body fat at the time of duty in SEA and change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin.

[c] Adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, and covariates specified under "Covariate Remarks" column.

Note: RH = Ranch Hand.
Comparison: Current Dioxin ≤ 10 ppt.
Background (Ranch Hand): Current Dioxin ≤ 10 ppt.
Low (Ranch Hand): Current Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 143 ppt.
High (Ranch Hand): Current Dioxin > 10 ppt, Initial Dioxin > 143 ppt.

Table 19-30. (Continued)
Analysis of Lupus Panel: Summary Index

g) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — UNADJUSTED					
	Current Dioxin Category Percent Abnormal/(n)			Analysis Results for Log_2 (Current Dioxin + 1)	
Model[a]	Low	Medium	High	Est. Relative Risk (95% C.I.)[b]	p-Value
4	39.9 (288)	41.5 (294)	30.7 (293)	0.90 (0.82,0.99)	0.028
5	39.6 (293)	42.6 (291)	29.9 (291)	0.92 (0.85,1.00)	0.042
6[c]	39.7 (292)	42.6 (291)	29.9 (291)	0.91 (0.83,0.99)	0.030

h) MODELS 4, 5, AND 6: RANCH HANDS — CURRENT DIOXIN — ADJUSTED				
	Analysis Results for Log_2 (Current Dioxin + 1)			
Model[a]	n	Adj. Relative Risk (95% C.I.)[b]	p-Value	Covariate Remarks
4	874	0.94 (0.85,1.04)	0.248	AGE ($p<0.001$) PACKYR ($p=0.068$)
5	874	0.95 (0.88,1.04)	0.259	AGE ($p<0.001$) PACKYR ($p=0.067$)
6[d]	873	0.95 (0.87,1.04)	0.294	AGE ($p<0.001$) PACKYR ($p=0.061$)

[a] Model 4: Log_2 (lipid-adjusted current dioxin + 1).
Model 5: Log_2 (whole-weight current dioxin + 1).
Model 6: Log_2 (whole-weight current dioxin + 1), adjusted for log_2 total lipids.

[b] Relative risk for a twofold increase in current dioxin.

[c] Adjusted for log_2 total lipids.

[d] Adjusted for log_2 total lipids in addition to covariates specified under "Covariate Remarks" column.

Note: Model 4: Low = ≤ 8.1 ppt; Medium = >8.1-20.5 ppt; High = >20.5 ppt.
Models 5 and 6: Low = ≤ 46 ppq; Medium = >46-128 ppq; High = >128 ppq.

Table 19-31.
Longitudinal Analysis of CD4-CD8 Ratio

a) MODEL 1: RANCH HANDS VS. COMPARISONS							
		Mean[a]/(n) Examination					
Occupational Category	Group	1985	1987	1992	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
All	***Ranch Hand***	***1.635 (303)***	***1.951 (284)***	***1.552 (303)***	***-0.083***	***0.029***	***0.109***
	Comparison	***1.600 (401)***	***1.903 (386)***	***1.488 (401)***	***-0.112***		
Officer	Ranch Hand	1.640 (126)	1.910 (120)	1.553 (126)	-0.087	0.007	0.534
	Comparison	1.591 (144)	1.934 (137)	1.498 (144)	-0.093		
Enlisted Flyer	Ranch Hand	1.570 (58)	1.959 (55)	1.493 (58)	-0.078	0.007	0.536
	Comparison	1.497 (69)	1.845 (67)	1.413 (69)	-0.084		
Enlisted Groundcrew	Ranch Hand	1.662 (119)	1.992 (109)	1.579 (119)	-0.082	0.056	0.227
	Comparison	1.647 (188)	1.902 (182)	1.509 (188)	-0.138		

[a] Transformed from natural logarithm scale.

[b] Difference between 1992 and 1985 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of CD4-CD8 ratio; results adjusted for natural logarithm of CD4-CD8 ratio in 1985 and age in 1992.

Note: Summary statistics for 1987 are provided for reference purposes for participants who attended the 1985, 1987, and 1992 examinations.

Table 19-31. (Continued)
Longitudinal Analysis of CD4-CD8 Ratio

b) MODEL 2: RANCH HANDS — INITIAL DIOXIN					
Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]	
Initial Dioxin	Mean[a]/(n) Examination 1985	1987	1992	Adj. Slope (Std. Error)	p-Value
Low	1.675 (52)	1.942 (50)	1.535 (52)	-0.0086 (0.0165)	0.602
Medium	1.654 (58)	2.139 (56)	1.656 (58)		
High	1.627 (64)	1.935 (56)	1.577 (64)		

[a] Transformed from natural logarithm scale.

[b] Results based on difference between natural logarithm of CD4-CD8 ratio in 1985 and natural logarithm of CD4-CD8 ratio in 1992 versus log_2 (initial dioxin); results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of blood draw for dioxin, natural logarithm of 1985 CD4-CD8 ratio, and age in 1992.

Note: Low = 39-98 ppt; Medium = >98-232 ppt; High = >232 ppt.
Summary statistics for 1987 are provided for reference purposes for participants who attended the 1985, 1987, and 1992 examinations.

Table 19-31. (Continued)
Longitudinal Analysis of CD4-CD8 Ratio

c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY						
	Mean[a]/(n) Examination					
Dioxin Category	1985	1987	1992	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
Comparison	1.590 (359)	1.896 (350)	1.478 (359)	-0.112		
Background RH	1.609 (117)	1.863 (112)	1.483 (117)	-0.126	-0.014	0.624
Low RH	1.643 (78)	1.991 (76)	1.565 (78)	-0.078	0.034	0.087
High RH	1.656 (96)	2.018 (86)	1.610 (96)	-0.047	0.066	0.303
Low plus High RH	1.650 (174)	2.005 (162)	1.590 (174)	-0.061	0.051	0.078

[a] Transformed from natural logarithm scale.

[b] Difference between 1992 and 1985 examination means after transformation to original scale.

[c] P-value is based on analysis of natural logarithm of CD4-CD8 ratio; results adjusted for percent body fat at the time of duty in SEA, change in percent body fat from the time of duty in SEA to the date of the blood draw for dioxin, natural logarithm of CD4-CD8 ratio in 1985, and age in 1992.

Note: RH = Ranch Hand.
Comparison: Current Dioxin $\leq$10 ppt.
Background (Ranch Hand): Current Dioxin $\leq$10 ppt.
Low (Ranch Hand): Current Dioxin $>$10 ppt, 10 ppt $<$ Initial Dioxin $\leq$143 ppt.
High (Ranch Hand): Current Dioxin $>$10 ppt, Initial Dioxin $>$143 ppt.
Summary statistics for 1987 are provided for reference purposes for participants who attended the 1985, 1987, and 1992 examinations.

The Model 3 longitudinal analysis exploring differences of examination mean change between 1985 and 1992 for the CD4-CD8 ratio disclosed marginally significant differences for low Ranch Hands versus Comparisons and low plus high Ranch Hands versus Comparisons (Table 19-31(c): p=0.087, Diff. of Exam. Mean Change=0.034 and p=0.078 Diff. of Exam. Mean Change=0.051 respectively). These results indicated that the decrease in the CD4-CD8 ratio between 1985 and 1992 was greater for Comparisons than for Ranch Hands. Between 1985 and 1992, differences in CD4-CD8 ratio for background and high Ranch Hands did not differ significantly from Comparisons.

DISCUSSION

Immunologic competence was assessed by analyzing data from skin tests for delayed hypersensitivity response, cell surface marker studies on a randomized subset of the study population, immunoglobulin quantitation, and autoantibody detection. The absence of a response to a series of skin test antigens is usually indicative of an impaired immune defense mechanism (anergy). Anergy can occur in elderly individuals in the setting of certain viral, bacterial, and fungal infections or with advanced protein deficiency, underlying malignancy, or treatment with corticosteroids, other immunosuppressive agents, or chemotherapy. Skin tests for delayed cutaneous hypersensitivity (DCH) are occasionally used to test for anergy as a prognostic indicator in individuals in compromised states such as those with AIDS or those at risk of infection following surgery.

Evaluation of the human immune system is divided into separate segments for humoral and cellular immunity. Circulating in the plasma phase of blood, the humoral segment consists of the immunoglobulin and complement proteins, some of which are also prominent at exposed sites of the body such as mucosal surfaces. The serum immunoglobulins are secreted by plasma cells in the bone marrow and are regulated in a sequence of events modulated by macrophages and memory lymphocytes. The immunoglobulins serve as a defense against bacterial infections and the blood-borne phase of viral infections.

Quantitative analysis of IgA, IgG, and IgM, give an overall view of B-cell integrity when related to the expected reference range of values. Selective deficiency of one or more of these antibody classes, whether congenital or acquired, may be associated with increased susceptibility to infections. Elevations of these immunoglobulins in a polyclonal pattern are frequently an indication of chronic infections (perhaps due to 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 cirrhosis. Selective elevation of a monoclonal segment of any immunoglobulin (detected by visual examination of serum protein electrophoresis as B cell clones) is a strong indicator of faulty regulation or actual autonomy of plasma cells or lymphocytes and may be an early hallmark of numerous conditions including plasmacytoma, multiple myeloma, chronic lymphocytic leukemia and lymphoma, and smoldering myeloma. Occasionally there may be a cluster of more than one small spike of immunoglobulin in the presence of other normal immunoglobulins. Invariably, this type of oligoclonal banding is associated with some alteration of the immune system (e.g., primary bone marrow involvement, inappropriate regulation, or immunosuppression as in organ transplant recipients). Thus, both quantitative and qualitative parameters of the serum immunoglobulins can give information on the integrity of B-cell responses.

Further evidence for the integrity of the immune system in aging individuals is the presence or absence of various autoantibodies. These autoantibodies measured in the lupus panel are considered to be abnormalities when present. While they can be specific and sensitive markers for autoimmune diseases (especially at high titers), they also occur as almost renegade substances when the immune system ages and as such are markers for deterioration of the B-cell regulatory process of immunity.

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 infectious history of individuals is usually sufficient to ascertain whether granulocytic deficiency is a consideration. Chapter 16, Hematologic Assessment, discusses the effect of dioxin on the components of these cells.

The lymphocytic segment of the immune response can be broadly evaluated by skin testing against multiple fungal, bacterial, or viral agents. The response to skin tests is dependent in part on the infection exposure history of the patient, and so is probably better used in the diagnosis of specific diseases than in an overall examination of lymphocyte function, although it does have the particular merit of demonstrating the presence or absence of the response in vivo, where it must be effective for the patient to remain healthy.

The total number of circulating lymphocytes provides information relative to the basic cellular quantity of cells present and available in the body for mounting an immune response. Examination of the surface marker proteins on the surfaces of these lymphocytes by flow cytometry is an excellent means of evaluating whether the regulatory interactions between T cells, B cells, and monocytes are intact. An alteration in the percentages of any of these categories 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, which is further broken down into the subpopulations of CD4 (helper cells) and CD8 (suppressor cells); CD4 and CD8 should be mutually exclusive. The ratio of CD4 to CD8 describes whether the regulation is in balance. Expected values for the CD4 to CD8 ratio are roughly 0.9 to 3.5. Ratios substantially below 1.0 are to be expected in patients immunosuppressed with cyclosporine and also those with active human immunodeficiency virus infection that involves primarily the CD4 positive cells. Activation of T cells results in the new synthesis of IL-2 receptor molecules on the surface of lymphocytes. This IL-2 receptor also is designated CD25, and its presence in excess is an indicator of recent stimulus to the immune system by virtually any type of antigen—for example, infectious organisms or transplanted organs. The surface marker for B cell CD20 gives an indication of the balance between cellular immunity and the ability to mount a B-cell response with production of specific antibodies. The CD14 marker is specific for monocytes that are essential for the correct transfer of stimulatory information from the (foreign) antigen processing segment to the antibody turn-on segment of a B-cell response. The CD5 marker frequently is found on abnormal subsets of B cells that predominate in chronic lymphocytic leukemia or that are responsible for autoimmune disease. The CD16 and CD56 markers are found on natural killer (NK) lymphocytes that provide a strong line of defense against the growth of neoplasms. Various combinations of these markers also were studied to detect double labeled cells that could indicate abnormalities such as very immature lymphocytes (e.g., CD4

with CD8, which should be mutually exclusive subsets). Additional double labeled studies were configured to provide better resolution of normal subsets (e.g., CD3 with CD25 to focus on true T cells that are activated).

Interpretation of alterations in the relative amounts of B cells, T cells and 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 IL-2 have even greater capacity to attack and destroy foreign cells. NK cells have still greater destructive capacity, but they act on a nonspecific basis and are probably simply recruited into regions of foreign antigens and tumors by the other recognition factors.

The immunologic evaluation performed on study participants went far beyond typical medical examinations employed for general health assessments. This evaluation included elements of measurement frequently used individually to define specific diseases. 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.

This thorough evaluation of the immune system did not reveal any relationships between dioxin exposure and physiologic abnormalities that could be considered clinically significant. Some individual elements showed statistical significance, although the magnitude of such relationships was small and certainly not to be interpreted as conveying health risk. An inverse relationship was found with dioxin exposure and the presence of autoantibodies to MSK smooth muscle, rheumatoid factor, and the lupus panel summary index. Although a negative test is usually considered to be normal, it is likely that a certain percentage of individuals would test as positive. The statistically significant negative association may indicate a highly sensitive but clinically insignificant first indication of a generalized immune suppression. Clarification of the relevance of these findings to a hypothesis of dioxin-induced immune suppression will require analysis of data from future physical examinations.

Conversely, because a normally active immune system does show development of some autoantibodies with age, finding fewer than expected autoantibodies may reflect some diminished capacity of the immune system to respond to stimuli. This interpretation is not typically evoked in otherwise healthy individuals; however, in this population study, fewer than expected autoantibodies may be a highly sensitive indication of immune suppression secondary to dioxin exposure. This issue cannot be resolved in the current cycle of study but should be evaluated in future examinations to determine clinical significance, if any.

Other findings correlating with dioxin exposure, including low IgG, presence of thyroid microsomal antibody, and alterations in lymphocyte surface markers, were also difficult to attribute to specific clinical deficiencies, because they were mild variations. A mild relationship between serum IgA concentrations and dioxin continued from the previous study in 1987. Although the magnitude of this effect was small, its statistical significance coupled

with continuity over time suggests a possible relationship that should be further evaluated because elevated IgA may indicate liver disease, chronic inflammation, or selective immune dysfunction (albeit mild).

In many instances, statistical correlations exist 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. Recent work has demonstrated the particular effect of tobacco use on the immune response (53-57).

In summary, these findings do not provide evidence of a clinically significant dose-response effect for body burden of dioxin on parameters of immunologic assessment. The minor statistically significant relationships that do have a small magnitude bear long-term evaluation for trend development, but at present they cannot be interpreted to indicate specific health impairment due to immune system dysfunction.

SUMMARY

The immunology assessment was based on physical examination data and laboratory data. Each of the variables was analyzed for associations with group (Model 1), initial lipid-adjusted dioxin (Model 2), categorized initial dioxin (Model 3), current lipid-adjusted dioxin (Model 4), and current whole-weight dioxin (Models 5 and 6). Tables 19-32 through 19-35 summarize the results. A summary of group-by-covariate and dioxin-by-covariate interactions is provided in Table 19-36.

Model 1: Group Analyses

In the unadjusted analyses of Model 1, the immunoglobulin IgG and the lupus panel ANA test showed marginally significant inverse relationships with group. The lupus panel thyroid microsomal antibody showed a significant positive association with group. The officer Ranch Hands had significantly or marginally significantly higher mean CD3 cell, CD4 cell, and CD5 cell counts than the officer Comparisons. The enlisted flyer Ranch Hands had marginally significantly lower mean CD8 cell and CD16+56 cell counts than the enlisted flyer Comparisons. CD5 with CD20 double labelled cells for measurements above zero showed enlisted groundcrew Ranch Hands to have significantly higher mean CD5 with CD20 values than the enlisted groundcrew Comparisons. The enlisted groundcrew Ranch Hands had a marginally significantly lower percentage of positive ANA test results than the enlisted groundcrew Comparisons.

Adjusting for covariates in Model 1 revealed a marginally significant positive association between group and CD20 cells and significant inverse associations between group and the immunoglobulin IgG and group and the lupus panel ANA test. Officer Ranch Hands had a marginally higher percentage of abnormal findings for the composite skin test diagnosis and the lupus panel MSK parietal antibody than the officer Comparisons. The officer Ranch Hands had a significantly lower percentage of positive rheumatoid factor findings than the officer Comparisons. The enlisted flyer Ranch Hands had significantly or marginally significantly lower mean CD8 cell, CD14 cell, CD25 cell, and CD3 with CD25 cell values

Table 19-32.
Summary of Group Analyses (Model 1) for Immunology Variables
(Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Physical Examination				
Composite Skin Test Diagnosis (D)	NS	NS	NS	NS
Laboratory: Cell Surface Marker				
CD3 Cells (C)	NS	+0.039	ns	NS
CD4 Cells (C)	NS	NS*	ns	NS
CD5 Cells (C)	NS	+0.035	NS	NS
CD8 Cells (C)	ns	NS	ns*	NS
CD14 Cells (C)	ns	NS	ns	ns
CD16+56 Cells (C)	ns	NS	ns*	ns
CD20 Cells (C)	NS	NS	ns	NS
CD25 Cells (C)	NS	NS	ns	NS
CD4-CD8 Ratio (C)	NS	NS	NS	NS
Double Labelled Cells: CD3 with CD25 (C)	NS	NS	ns	NS
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	NS	NS	ns	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS	NS	ns	+0.046
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	NS	ns
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	ns	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	NS	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	NS	NS	NS	ns
Laboratory: TLC				
TLC (C)	NS	NS	ns	NS
Laboratory: Immunoglobulins				
IgA (C)	ns	ns	ns	NS
IgG (C)	ns*	ns	ns	ns
IgM (C)	ns	NS	ns	ns

Table 19-32. (Continued)
Summary of Group Analyses (Model 1) for Immunology Variables
(Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Laboratory:				
Lupus Panel				
ANA Test (D)	ns*	ns	ns	ns*
Thyroid Microsomal Antibody (D)	NS*	NS	NS	NS
MSK Smooth Muscle Antibody (D)	ns	NS	ns	ns
MSK Mitochondrial Antibody (D)	ns	NS	--	ns
MSK Parietal Antibody (D)	ns	NS	ns	ns
Rheumatoid Factor (D)	ns	ns	ns	NS
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS	NS	NS	ns
Other Antibodies (ANA and MSK) (D)	ns	ns	ns	ns
Summary Index (D)	ns	ns	ns	ns

C: Continuous analysis.
D: Discrete analysis.
+: Difference of means nonnegative for continuous analysis.
--: Analysis not presented due to sparse number of abnormalities.
NS or ns: Not significant ($p > 0.10$).
NS* or ns*: Marginally significant ($0.05 < p \leq 0.10$).
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 19-32. (Continued)
Summary of Group Analyses (Model 1) for Immunology Variables
(Ranch Hands vs. Comparisons)

Variable	ADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Physical Examination				
Composite Skin Test Diagnosis (D)	NS	NS*	NS	NS
Laboratory: Cell Surface Marker				
CD3 Cells (C)	NS	NS	ns	NS
CD4 Cells (C)	NS	NS	ns	NS
CD5 Cells (C)	NS	NS	ns	NS
CD8 Cells (C)	ns	NS	ns*	NS
CD14 Cells (C)	**(ns)	NS	-0.021	NS
CD16+56 Cells (C)	ns	NS	ns	ns
CD20 Cells (C)	**(NS*)	**(NS)	**(ns)	**(NS)
CD25 Cells (C)	**(NS)	NS	-0.015	NS
CD4-CD8 Ratio (C)	**(NS)	**(NS)	**(NS)	**(NS)
Double Labelled Cells: CD3 with CD25 (C)	**(NS)	NS	-0.022	NS
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	NS	NS	ns	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS	NS	ns	NS
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	NS	ns
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	ns	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	NS	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	ns	NS	ns	ns
Laboratory: TLC				
TLC (C)	NS	NS	ns	NS
Laboratory: Immunoglobulins				
IgA (C)	ns	ns	NS	NS
IgG (C)	ns*	ns	ns	ns
IgM (C)	**(ns)	**(NS)	**(ns)	**(ns)

Table 19-32. (Continued)
Summary of Group Analyses (Model 1) for Immunology Variables
(Ranch Hands vs. Comparisons)

Variable	ADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Laboratory:				
Lupus Panel				
ANA Test (D)	ns*	ns	ns	ns*
Thyroid Microsomal Antibody (D)	****	****	****	****
MSK Smooth Muscle Antibody (D)	ns	NS	ns	ns
MSK Mitochondrial Antibody (D)	--	--	--	--
MSK Parietal Antibody (D)	**(ns)	**(NS*)	**(NS)	**(NS)
Rheumatoid Factor (D)	ns	ns*	ns	NS
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS	NS	NS	ns
Other Antibodies (ANA and MSK) (D)	ns	ns	ns	ns
Summary Index (D)	ns	ns	ns	ns

C: Continuous analysis.
D: Discrete analysis.
-: Difference of means negative for continuous analysis.
--: Analysis not performed due to sparse number of abnormalities.
NS or ns: Not significant ($p > 0.10$).
NS* or ns*: Marginally significant ($0.05 < p \leq 0.10$).
**(NS) or **(ns): Group-by-covariate interaction ($p \leq 0.05$); not significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(NS*): Group-by-covariate interaction ($p \leq 0.05$); marginally significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**** Group-by-covariate interaction ($p \leq 0.01$); refer to Appendix 0-2 for further analysis of this interaction.
Note: A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 19-33.
Summary of Initial Dioxin Analyses (Model 2) for Immunology Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Physical Examination		
Composite Skin Test Diagnosis (D)	ns	ns
Laboratory: Cell Surface Markers		
CD3 Cells (C)	NS	**(ns)
CD4 Cells (C)	NS	ns
CD5 Cells (C)	NS	**(ns)
CD8 Cells (C)	NS	****
CD14 Cells (C)	NS	NS
CD16+56 Cells (C)	ns	**(NS)
CD20 Cells (C)	NS*	**(ns)
CD25 Cells (C)	NS	ns
CD4-CD8 Ratio (C)	NS	ns
Doubled Labelled Cells: CD3 with CD25 (C)	NS	ns
Doubled Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	ns	ns*
Doubled Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS	ns
Doubled Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	ns	**(ns)
Doubled Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	NS	**(NS)
Doubled Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	NS*	****
Doubled Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	ns*	ns
Laboratory: TLC		
TLC (C)	NS	****
Laboratory: Immunoglobulins		
IgA (C)	NS	NS*
IgG (C)	NS	ns
IgM (C)	NS	NS

Table 19-33. (Continued)
Summary of Initial Dioxin Analyses (Model 2) for Immunology Variables
(Ranch Hands Only)

Variable	Unadjusted	Adjusted
Laboratory:		
Lupus Panel		
ANA Test (D)	ns	NS
Thyroid Microsomal Antibody (D)	ns	**(ns)
MSK Smooth Muscle Antibody (D)	-0.035	-0.022
MSK Mitochondrial Antibody (D)	-0.030	--
MSK Parietal Antibody (D)	ns	ns
Rheumatoid Factor (D)	-0.028	**(ns*)
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS	NS
Other Antibodies (ANA and MSK) (D)	NS	NS
Summary Index (D)	ns*	ns

C: Continuous analysis.
D: Discrete analysis.
-: Relative risk < 1.00 for discrete analysis.
--: Analysis not performed due to sparse number of abnormalities.
NS or ns: Not significant ($p > 0.10$).
NS* or ns*: Marginally significant ($0.05 < p \leq 0.10$).
**(NS) or **(ns): Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.05$); not significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(ns*): Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.05$); marginally significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**** Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); refer to Appendix O-2 for further analysis of this interaction.
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

Table 19-34.
Summary of Categorized Dioxin Analyses (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
Physical Examination				
Composite Skin Test Diagnosis (D)	+0.024	NS	ns	NS
Laboratory: Cell Surface Markers				
CD3 Cells (C)	NS	ns	NS	NS
CD4 Cells (C)	NS	ns	NS	NS
CD5 Cells (C)	NS	ns	NS	NS
CD8 Cells (C)	NS	ns	ns	ns
CD14 Cells (C)	NS	-0.033	ns	ns*
CD16+56 Cells (C)	ns	ns	ns	ns
CD20 Cells (C)	NS	ns	NS	NS
CD25 Cells (C)	NS	ns	NS	NS
CD4-CD8 Ratio (C)	NS	NS	NS	NS
Double Labelled Cells: CD3 with CD25 (C)	NS	NS	NS	NS
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	ns	NS	ns	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	ns	NS	NS*	NS
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	NS	NS
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	NS	ns	ns	ns
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	ns	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	NS	NS	ns	ns
Laboratory: TLC				
TLC (C)	NS	ns	NS	ns

Table 19-34. (Continued)
Summary of Categorized Dioxin Analyses (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: Immunoglobulins				
IgA (C)	ns	ns	ns	ns
IgG (C)	ns	ns	ns	ns
IgM (C)	NS	ns	ns	ns
Laboratory: Lupus Panel				
ANA Test (D)	ns	ns	-0.030	-0.047
Thyroid Microsomal Antibody (D)	NS	+0.020	NS	+0.016
MSK Smooth Muscle Antibody (D)	NS	NS	ns*	ns
MSK Mitochondrial Antibody (D)	NS	NS	--	ns
MSK Parietal Antibody (D)	ns	NS	ns	NS
Rheumatoid Factor (D)	ns	NS	-0.012	ns
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS*	ns	NS	ns
Other Antibodies (ANA and MSK) (D)	ns	ns	ns	ns
Summary Index (D)	ns	ns	-0.002	-0.021

C: Continuous analysis.
D: Discrete analysis.
+: Difference of means nonnegative for continuous analysis.
-: Relative risk < 1.00 for discrete analysis or difference of means negative for continuous analysis.
--: Analysis not presented due to sparse number of abnormalities.
NS or ns: Not significant ($p > 0.10$).
NS* or ns*: Marginally significant ($0.05 < p \leq 0.10$).
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 19-34. (Continued)
Summary of Categorized Dioxin Analyses (Model 3) for Immunology Variables (Ranch Hands vs. Comparisons)

Variable	ADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Physical Examination				
Composite Skin Test Diagnosis (D)	**(+0.047)	**(NS)	**(ns)	**(NS)
Laboratory: Cell Surface Markers				
CD3 Cells (C)	**(NS)	**(ns)	**(NS)	**(NS)
CD4 Cells (C)	**(NS)	**(ns)	**(NS)	**(NS)
CD5 Cells (C)	**(NS)	**(ns)	**(NS)	**(NS)
CD8 Cells (C)	**(NS)	**(ns)	**(ns)	**(ns)
CD14 Cells (C)	****	****	****	****
CD16+56 Cells (C)	**(ns)	**(ns*)	**(ns)	**(ns*)
CD20 Cells (C)	+0.013	NS	NS	NS
CD25 Cells (C)	**(NS)	**(ns)	**(NS)	**(NS)
CD4-CD8 Ratio (C)	NS	NS	NS	NS*
Double Labelled Cells: CD3 with CD25 (C)	**(NS)	**(ns)	**(NS)	**(NS)
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	ns	NS	NS	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS	NS	NS	NS
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	ns	NS
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	**(NS)	**(ns)	**(ns)	**(ns)
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	ns	ns	NS	NS
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	NS	NS	ns	ns
Laboratory: TLC				
TLC (C)	**(NS)	**(ns)	**(NS)	**(ns)

Table 19-34. (Continued)
Summary of Categorized Dioxin Analyses (Model 3) for Immunology Variables (Ranch Hands vs. Comparisons)

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: Immunoglobulins				
IgA (C)	**(ns)	**(ns)	**(ns)	**(ns)
IgG (C)	**(ns)	**(ns)	**(ns)	**(ns*)
IgM (C)	****	****	****	****
Laboratory: Lupus Panel				
ANA Test (D)	****	****	****	****
Thyroid Microsomal Antibody (D)	****	****	****	****
MSK Smooth Muscle Antibody (D)	NS	NS	ns	ns
MSK Mitochondrial Antibody (D)	--	--	--	--
MSK Parietal Antibody (D)	ns	NS	NS	NS
Rheumatoid Factor (D)	**(ns)	**(NS)	**(-0.035)	**(ns)
B Cell Clones Detected by Serum Protein Electrophoresis (D)	NS	ns	NS	ns
Other Antibodies (ANA and MSK) (D)	ns	ns	ns	ns
Summary Index (D)	ns	ns	-0.019	-0.040

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00 for discrete analysis or difference of means nonnegative for continuous analysis.
-: Relative risk $<$ 1.00 for discrete analysis.
--: Analysis not performed due to sparse number of abnormalities.
NS or ns: Not significant ($p > 0.10$).
NS*: Marginally significant ($0.05 < p \leq 0.10$).
**(NS) or **(ns*): Categorized dioxin-by-covariate interaction ($p \leq 0.05$); not significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(ns*): Categorized dioxin-by-covariate interaction ($p \leq 0.05$); marginally significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(0.035): Categorized dioxin-by-covariate interaction ($p \leq 0.05$); significant ($p = 0.035$) when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**** Categorized dioxin-by-covariate interaction ($p \leq 0.01$); refer to Appendix O-2 for further analysis of this interaction.
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 19-35.
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Immunology Variables (Ranch Hands Only)

Variable	UNADJUSTED		
	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Physical Examination			
Composite Skin Test Diagnosis (D)	-0.008	-0.012	-0.014
Laboratory: Surface Cell Markers			
CD3 Cells (C)	ns	ns	ns
CD4 Cells (C)	NS	NS	ns
CD5 Cells (C)	NS	NS	ns
CD8 Cells (C)	ns	ns	ns
CD14 Cells (C)	ns	NS	ns
CD16+56 Cells (C)	ns	ns	ns
CD20 Cells (C)	NS	NS	NS
CD25 Cells (C)	ns	ns	ns
CD4-CD8 Ratio (C)	NS	NS	NS
Double Labelled Cells: CD3 with CD25 (C)	ns	ns	ns
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	NS	NS	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	+0.017	+0.016	+0.044
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	NS	NS	NS
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	ns	ns	ns
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	+0.024	+0.010	+0.042
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	-0.014	-0.009	ns*
Laboratory: TLC			
TLC (C)	NS	NS	ns
Laboratory: Immunoglobulins			
IgA (C)	NS	NS	NS*
IgG (C)	NS	ns	NS
IgM (C)	NS	ns	NS

Table 19-35. (Continued)
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Immunology Variables (Ranch Hands Only)

Variable	UNADJUSTED		
	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Laboratory: Lupus Panel			
ANA Test (D)	ns	ns	ns*
Thyroid Microsomal Antibody (D)	NS	NS	NS
MSK Smooth Muscle Antibody (D)	ns*	ns	ns*
MSK Mitochondrial Antibody (D)	ns	ns	ns
MSK Parietal Antibody (D)	NS	NS	NS
Rheumatoid Factor (D)	-0.038	-0.023	ns
B Cell Clones Detected by Serum Protein Electrophoresis (D)	ns	ns	ns
Other Antibodies (ANA and MSK) (D)	NS	NS	NS
Summary Index (D)	-0.028	-0.042	-0.030

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk $\geq$ 1.00 for discrete analysis or slope nonnegative for continuous analysis.
-: Relative risk $<$ 1.00 for discrete analysis or slope negative for continuous analysis.
NS or ns: Not significant ($p > 0.10$).
NS* or ns*: Marginally significant ($0.05 < p \leq 0.10$).
Note: 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 lower case "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

Table 19-35. (Continued)
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Immunology Variables (Ranch Hands Only)

Variable	ADJUSTED		
	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Physical Examination			
Composite Skin Test Diagnosis (D)	-0.029	-0.037	**(-0.047)
Laboratory: Surface Cell Markers			
CD3 Cells (C)	ns	NS	ns
CD4 Cells (C)	NS	NS	ns
CD5 Cells (C)	NS	NS	ns
CD8 Cells (C)	**(ns)	ns	ns
CD14 Cells (C)	ns	NS	ns
CD16+56 Cells (C)	NS	ns	NS
CD20 Cells (C)	NS	NS	NS
CD25 Cells (C)	ns	NS	**(ns)
CD4-CD8 Ratio (C)	NS	NS	ns
Double Labelled Cells: CD3 with CD25 (C)	ns	NS	**(ns)
Double Labelled Cells: CD5 with CD20 (D: Zero vs. Nonzero)	NS	NS	NS
Double Labelled Cells: CD5 with CD20 (C: Nonzero Measurements)	NS*	+0.044	NS
Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	ns	ns	ns
Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	ns	NS	ns
Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	****	****	****
Double Labelled Cells: CD3 with CD16+56 (C: Nonzero Measurements)	-0.040	-0.032	ns
Laboratory: TLC			
TLC (C)	NS	NS	NS
Laboratory: Immunoglobulins			
IgA (C)	NS	NS	NS
IgG (C)	ns	ns	ns
IgM (C)	**(ns)	ns	NS

Table 19-35. (Continued)
Summary of Current Dioxin Analyses (Models 4, 5, and 6) for Immunology Variables (Ranch Hands Only)

Variable	ADJUSTED		
	Model 4: Lipid-Adjusted Current Dioxin	Model 5: Whole-Weight Current Dioxin	Model 6: Whole-Weight Current Dioxin Adjusted for Total Lipids
Laboratory: Lupus Panel			
ANA Test (D)	**(ns)	**(ns)	**(ns)
Thyroid Microsomal Antibody (D)	**(NS)	NS	NS
MSK Smooth Muscle Antibody (D)	ns	ns	ns
MSK Mitochondrial Antibody (D)	--	--	--
MSK Parietal Antibody (D)	NS	NS	NS
Rheumatoid Factor (D)	-0.013	-0.008	ns*
B Cell Clones Detected by Serum Protein Electrophoresis (D)	ns	**(ns)	**(ns)
Other Antibodies (ANA and MSK) (D)	NS	NS	**(NS)
Summary Index (D)	ns	ns	ns

C: Continuous analysis.
D: Discrete analysis.
+: Slope nonnegative for continuous analysis.
-: Relative risk < 1.00 for discrete analysis or slope negative for continuous analysis.
--: Analysis not performed due to sparse number of abnormalities.
NS or ns: Not significant ($p > 0.10$).
NS* or ns*: Marginally significant ($0.05 < p \leq 0.10$).
**(NS) or **(ns): Log_2 (current dioxin + 1)-by-covariate interaction ($p \leq 0.05$); not significant when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**(0.047): Log_2 (current dioxin + 1)-by-covariate interaction ($p \leq 0.05$); significant ($p = 0.047$) when interaction is deleted; refer to Appendix O-2 for further analysis of this interaction.
**** Log_2 (current dioxin + 1)-by-covariate interaction ($p \leq 0.01$); refer to Appendix O-2 for a detailed description of this interaction.
Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or a nonnegative slope for continuous analysis; a lower case "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

Table 19-36.
Summary of Group-by-Covariate and Dioxin-by-Covariate Interactions from Adjusted Analyses of Immunology Variables

Model	Variable	Covariate
1[a]	CD14 Cells	Occupation
	CD20 Cells	Lifetime Alcohol History
	CD25 Cells	Occupation
	CD4-CD8 Ratio	Physical Activity Index
	Double Labelled Cells: CD3 with CD25 Cells	Occupation
	IgM	Race, Physical Activity Index
	Lupus Panel: Thyroid Microsomal Antibody	Current Cigarette Smoking, Current Alcohol Use, Lifetime Alcohol History
	Lupus Panel: Parietal Antibody	Race
2[b]	CD3 Cells	Occupation
	CD5 Cells	Occupation
	CD8 Cells	Occupation
	CD16+56 Cells	Occupation, Physical Activity Index
	CD20 Cells	Age
	Double Labelled Cells: CD4 with CD8 (D: Zero vs. Nonzero)	Race, Current Cigarette Smoking
	Double Labelled Cells: CD4 with CD8 (C: Nonzero Measurements)	Lifetime Alcohol History
	Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	Occupation
	TLC	Physical Activity Index
	Lupus Panel: Thyroid Microsomal Antibody	Current Cigarette Smoking, Lifetime Alcohol History
	Lupus Panel: Rheumatoid Factor	Age, Occupation
3[c]	Composite Skin Test Diagnosis	Current Alcohol Use
	CD3 Cells	Age, Occupation
	CD4 Cells	Age, Occupation
	CD5 Cells	Age, Occupation
	CD8 Cells	Age, Occupation
	CD14 Cells	Age
	CD16+56 Cells	Occupation, Lifetime Alcohol History, Physical Activity Index
	CD25 Cells	Age, Occupation, Lifetime Cigarette Smoking History, Lifetime Alcohol History

Table 19-36. (Continued)
Summary of Group-by-Covariate and Dioxin-by-Covariate Interactions from Adjusted Analyses of Immunology Variables

Model	Variable	Covariate
3[c]	Double Labelled Cells: CD3 with CD25 Cells	Occupation, Lifetime Cigarette Smoking History, Lifetime Alcohol History
	CD4 with CD8 (C: Nonzero Measurements)	Age, Race, Occupation
	TLC	Age
	IgA	Race
	IgG	Occupation
	IgM	Physical Activity Index
	Lupus Panel: Antinuclear Antibody (ANA)	Lifetime Alcohol History
	Lupus Panel: Thyroid Microsomal Antibody	Current Cigarette Smoking, Current Alcohol Use, Lifetime Alcohol History
	Lupus Panel: Rheumatoid Factor	Occupation, Physical Activity Index
4[d]	CD8 Cells	Occupation
	Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	Physical Activity Index
	IgM	Current Alcohol Use
	Lupus Panel: Antinuclear Antibody (ANA)	Race, Lifetime Alcohol History
	Lupus Panel: Thyroid Microsomal Antibody	Current Alcohol Use
5[e]	Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	Physical Activity Index
	Lupus Panel: Antinuclear Antibody (ANA)	Race, Lifetime Alcohol History
	Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis	Current Alcohol Use
6[f]	Composite Skin Test Diagnosis	Occupation
	CD25 Cells	Lifetime Cigarette Smoking History
	Double Labelled Cells: CD3 with CD25 Cells	Lifetime Cigarette Smoking History
	Double Labelled Cells: CD3 with CD16+56 (D: Zero vs. Nonzero)	Physical Activity Index
	Lupus Panel: Antinuclear Antibody (ANA)	Race, Lifetime Alcohol History
	Lupus Panel: B Cell Clones Detected by Serum Protein Electrophoresis	Current Alcohol Use
	Lupus Panel: Other Antibodies (ANA and MSK)	Race

C: Continuous analysis.
D: Discrete analysis.

[a] Group Analysis (Ranch Hands vs. Comparison).
[b] Ranch Hands—Log_2 (Initial Dioxin).
[c] Categorized Dioxin.
[d] Ranch Hands—Log_2 (Current Lipid-Adjusted Dioxin + 1).
[e] Ranch Hands—Log_2 (Current Whole-Weight Dioxin + 1).
[f] Ranch Hands—Log_2 (Current Whole-Weight Dioxin + 1), Adjusted for Total Lipids.

than the enlisted flyer Comparisons. The enlisted groundcrew Ranch Hands had a marginally significantly lower percentage of positive lupus panel ANA test findings than the enlisted groundcrew Comparisons.

Model 2: Initial Dioxin Analyses

In the unadjusted analysis of Model 2, marginally significant positive associations with initial dioxin were revealed for CD20 cells and the CD3 with CD16+56 double labelled cells when dichotomized as zero and nonzero. Significant or marginally significant inverse associations with initial dioxin were revealed for the MSK smooth muscle antibody, the lupus panel rheumatoid factor, the lupus panel summary index, and the analysis of nonzero measurements of CD3 with CD16+56 double labelled cells. The adjusted analysis revealed significant or marginally significant inverse associations between initial dioxin and MSK smooth muscle antibody, rheumatoid factor, and the discretized form (zero vs. nonzero) of CD5 with CD20 double labelled cells. A significant positive association between initial dioxin and IgA was revealed in the adjusted analysis.

Model 3: Categorized Dioxin Analyses

In Model 3, the unadjusted analyses of composite skin test diagnosis and B cell clones each revealed a significantly higher percentage of abnormalities in the background Ranch Hands than the Comparisons. The unadjusted analysis of CD14 cells showed the low Ranch Hands to have significantly lower mean CD14 cell counts than the Comparisons. However, the lupus panel thyroid microsomal antibody test showed the low Ranch Hands to have significantly higher positive findings than the Comparisons. A significantly or marginally significantly lower percentage of abnormalities were noted in the high Ranch Hands than the Comparisons for the lupus panel ANA test, MSK smooth muscle antibody, rheumatoid factor, and the lupus panel summary index. The high Ranch Hands exhibited a higher mean value than the Comparisons for the double labelled cells CD5 with CD20 for measurements above zero. The unadjusted analysis revealed significantly or marginally significantly lower values for the low plus high Ranch Hands than the Comparisons for CD14 cells, the lupus panel ANA test, and the lupus panel summary index. The low plus high Ranch Hands exhibited a significantly higher percentage of positive results for the lupus panel thyroid microsomal antibody than the Comparisons.

The adjusted analysis of Model 3 revealed a significantly higher percentage of composite skin test abnormalities in the background Ranch Hands than the Comparisons. Similarly, the mean CD20 cell count was higher in the background Ranch Hands than the Comparisons. The adjusted analysis of Model 3 revealed marginally significantly lower mean CD16+56 cell values in the low Ranch Hands than the Comparisons. The lupus panel rheumatoid factor test and the lupus panel summary index each showed a significantly lower percentage of positive findings in the high Ranch Hands than the Comparisons. The adjusted analysis of CD15+56 cells and immunoglobulin IgG revealed marginally significantly lower means in the low plus high Ranch Hands than the Comparisons. The percentage of abnormalities in the lupus panel summary index was significantly lower in the low plus high Ranch Hands than the Comparisons. A marginally significantly higher mean CD4 to CD8 ratio existed in the low plus high Ranch Hands than the Comparisons.

Models 4, 5, and 6: Current Dioxin Analyses

The unadjusted analysis of Models 4, 5, and 6 revealed significant or marginally significant inverse associations between current dioxin and composite skin test diagnosis, CD3 with CD16+56 double labelled cells with measurements above zero, and the lupus panel summary index. The unadjusted analysis of Models 4 through 6 showed positive relationships between current dioxin and the double labelled cells CD5 with CD20 with measurements above zero and the double labelled cells CD3 with CD16 with values dichotomized as zero and nonzero. The unadjusted analysis of Model 4 showed marginally significant or significant inverse associations with the lupus panel MSK smooth muscle antibody and rheumatoid factor. The lupus panel rheumatoid factor was inversely associated with current dioxin in Model 5. The unadjusted analysis for Model 6 revealed a marginally significant positive association between current dioxin and the immunoglobulin IgA. Model 6 also showed a marginally significant inverse relationship between current dioxin and the lupus panel ANA test and MSK smooth muscle antibody.

In the adjusted analysis of each of Models 4 through 6, the composite skin test diagnosis and lupus panel rheumatoid factor showed significant or marginally significant inverse relationships with current dioxin. In the adjusted analysis of Models 4 and 5, the nonzero double labelled cells CD5 with CD20 measurements showed a marginally significant or significant increase with current dioxin. The double labelled cells CD3 with CD16+56 for measurements above zero also displayed significant inverse relationships with current dioxin in Models 4 and 5.

CONCLUSION

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; however, the increased IgA levels could represent a chronic inflammatory response to dioxin exposure and thus suggest long-term evaluation.

The statistically significant inverse relationships revealed between dioxin and a few of the lupus panel autoantibodies also are inconsistent with a harmful effect from dioxin. The presence of these autoantibodies, such as MSK smooth muscle antibody, rheumatoid factor, and the lupus panel summary index, is generally considered to be abnormal. However, the presence of fewer than expected of these autoantibodies also may be abnormal. This may suggest a possible early immune alteration that may not carry clinical significance. These findings should be investigated and clarified in further followups.

The indices of immune responses analyzed in this chapter provided a comprehensive reflection of in vivo and in vitro immune function in the study population. No clinically significant indicators reflecting a consistent relationship between serum dioxin and deficiency in immune function were found.

CHAPTER 19
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