

# **AIR FORCE HEALTH STUDY**

## **FINAL REPORT**

*An Epidemiologic Investigation of  
Health Effects in Air Force Personnel  
Following Exposure to Herbicides*

### **VOLUME II**

**1997 Follow-up Examination Results  
May 1997 to February 2000**

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**Volume II**

**1997 Follow-up Examination Results**

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## 13 GASTROINTESTINAL ASSESSMENT

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### 13.1 INTRODUCTION

#### 13.1.1 Background

In contrast with the wealth of dioxin research data available in animal models, there is relatively little information about the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) on the human digestive system. Although the pharmacokinetics of orally ingested dioxin in a human volunteer have been reported (1), the pathologic lesions that have been studied in animals (gastric metaplasia with ulceration and ileitis) have not been described in human populations, in which the principal route of exposure has been transcutaneous. Further, in two reports of extreme phenoxyherbicide toxicity by ingestion in three humans, the primary target organs were the central nervous system with associated coma and the musculoskeletal system with rhabdomyolysis and renal failure, rather than the digestive system (2, 3).

The digestive system and, particularly, the liver (4-9) and stomach (5, 10-14) have been clearly defined as target organs for dioxin toxicity in numerous laboratory animals. Dioxin ingested by rodents (15-20) and adult monkeys (21) is absorbed by the intestinal lymphatics, transported by chylomicrons in the enterohepatic, and preferentially stored in adipose tissue and the liver. Hepatotoxic manifestations, which appear to be dose- and time-dependent, include cellular hypertrophy, parenchymal necrosis (principally centrilobular), fatty degeneration, and the production of altered hepatic foci, a microscopic precursor in hepatic carcinogenesis (9, 22-24). Chronic feeding studies have confirmed the role of dioxin as a hepatic carcinogen in rats (25, 26) and mice (27). Gastric endpoints have been the subject of several reports that have focused on histologic changes (5, 12, 13) and endocrine secretory abnormalities (10, 11, 28) associated with dioxin toxicity.

A host of hepatic biochemical reactions related to dioxin toxicity has been studied, including lipid peroxidation (29-33), hepatic prostaglandin synthetase activity (34), and inhibition of glutathione peroxidase (30). Results from several lines of biochemical investigation have created a bridge between animal and human studies including research into lipid (33, 35-37) and porphyrin metabolism (38-41). In rats, dioxin has been shown to increase the activity of glucuronyl transferase (42), an observation that led to the use of urinary d-glucaric acid as a marker for dioxin exposure in several human epidemiological studies (43-47). The most recent of these, and the only one to include serum dioxin levels, found no correlation between this index and the body burden of dioxin (47).

In published occupational and environmental studies, acid peptic disease is the only digestive disorder intrinsic to the gastrointestinal tract that has been examined in relation to dioxin exposure. The finding of an increased cumulative incidence of ulcer disease reported in two studies (48, 49) was not confirmed in others (47, 50). In the only occupational study to include serum dioxin levels, the cumulative incidence of gastritis, ulcer disease, and gastrointestinal hemorrhage was similar in exposed workers (mean serum dioxin of 220 picograms [pg] per gram of lipid) and controls (mean of 7 pg per gram of lipid) (47).

Numerous occupational and environmental studies have reported abnormally elevated liver enzymes in association with exposure to dioxin, although in most cases there was no other clinical evidence for underlying liver disease (47-54). In longer-term follow-up studies, abnormalities noted at the time of acute exposure resolved over time (46, 54-57). In two environmental contamination studies conducted in 1984-85 at Quail Run (46) and in 1983 at Times Beach (58), Missouri, there was no evidence for hepatic

enzyme elevations in association with exposure to dioxin. In the 1987-88 National Institute of Occupational Safety and Health study (47), the prevalence of an abnormally elevated liver enzyme gamma glutamyl transferase (GGT) was significantly higher in the exposed cohort, but the association was noted only in those with significant alcohol consumption and did not appear directly related to the body burden of dioxin. Three recently published occupational studies found no significant association between elevated hepatic enzymes and serum dioxin levels (59-61).

Several reports of Vietnam veterans have focused on the potential association of hepatic disease with herbicide exposure. In one retrospective cohort study, in which the self-reporting of a rash during or after duty in Vietnam was used as a surrogate for dioxin exposure, an increased prevalence of liver enzyme abnormalities was noted but was attributed to prior viral hepatitis and alcohol consumption (62). Similarly, chronic alcoholism contributed to increased mortality from digestive diseases (cirrhosis and peptic ulcer) in a study of United States Army Chemical Corps veterans (63). Finally, in the most recent reports of the Air Force Health Study (AFHS), which have included serum dioxin levels in the analyses, there has been no increase in the prevalence of biologically meaningful hepatic or digestive disease in the Ranch Hand versus the Comparison cohorts (64, 65), although GGT and alanine aminotransferase (ALT) have been found to increase with dioxin body burden in Ranch Hand veterans. For example, GGT was significantly increased in the high dioxin category at the 1992 follow-up examination.

### 13.1.2 Summary of Previous Analyses of the Air Force Health Study

#### *13.1.2.1 1982 Baseline Study Summary Results*

The 1982 AFHS examination included an extensive evaluation of hepatic status by questionnaire, physical examination, and laboratory testing. The questionnaire elicited data on liver conditions, liver disease, and symptoms compatible with porphyria cutanea tarda (PCT), as well as detailed information on PCT risk factors (e.g., alcohol consumption, chemical exposures). The physical examination measured hepatomegaly, or enlarged liver, when present and determined liver function and porphyrin patterns by a comprehensive battery of 12 laboratory tests.

The questionnaire showed that Ranch Hands reported more miscellaneous liver conditions (verified by a medical records review) and more skin changes compatible with PCT than their Comparisons. Although the reported skin changes were statistically significant, no cases of PCT were diagnosed at examination in either cohort.

Ranch Hands had significantly higher GGT and lactic dehydrogenase (LDH) means and lower cholesterol means; no differences were found for bilirubin or alkaline phosphatase means. There were no significant group differences in uroporphyrin, coproporphyrin, or d-aminolevulinic acid levels, nor did any test set support a diagnosis of PCT.

A comprehensive hepatic evaluation did not reveal any consistent pattern of significant liver damage in the Ranch Hand group.

#### *13.1.2.2 1985 Follow-up Study Summary Results*

The 1985 AFHS examination continued the emphasis on hepatic function and expanded the porphyrin test battery to six assays. The interval questionnaire revealed sparse reporting of liver disorders from 1982 to 1985. Reported liver diseases were verified by medical records, and these data were added to the verified baseline history to assess possible lifetime differences. No significant differences were found.

The physical examination disclosed a marginally significant increase of hepatomegaly in the Ranch Hand group. Emphasis was placed on nine laboratory test variables measuring liver functions: aspartate aminotransferase (AST), ALT, GGT, alkaline phosphatase, total and direct bilirubin, LDH, cholesterol, and triglycerides. In addition, uroporphyrin and coproporphyrin measurements were obtained to assess the likelihood of PCT.

Only four variables produced differences of any note. The results showed a significantly lower mean ALT level, a greater mean alkaline phosphatase level, a lower mean uroporphyrin level, and a marginally significant greater mean coproporphyrin level in Ranch Hands. The risk of alkaline phosphatase abnormality was marginally significantly increased in Ranch Hands.

Overall, the 1985 follow-up examination laboratory data showed no adverse clinical or exposure patterns. The continuous statistical tests detected significant mean shifts that were not mirrored by the discrete tests. These findings were generally consistent with the 1982 baseline examination data. Slight differences in analytic results probably were due to the use of more fully adjusted models for the 1985 follow-up examination data.

Interval reporting of PCT-like symptoms of skin patches, bruises, and sensitivity was significantly increased in Ranch Hands. When these historic data were contrasted to both uroporphyrin and coproporphyrin abnormalities, no correlation was apparent, nor were there any significant group differences. The likelihood of bona fide PCT among Ranch Hands appeared to be remote.

#### *13.1.2.3 1987 Follow-up Study Summary Results*

Overall, the gastrointestinal assessment did not find the health of the Ranch Hand group to be significantly different from that of the Comparison group. Group differences based on verified historical data from the questionnaire were not significant for eight categories of liver disease. No significant group difference was found for past or present occurrence of peptic ulcers. The prevalence of hepatomegaly diagnosed at the physical examination also was not significantly different between the two groups. The only significant finding from the laboratory examination variables was that Ranch Hands had a higher mean alkaline phosphatase than Comparisons, also noted at the 1985 follow-up examination. Group differences for the other laboratory variables (AST, ALT, GGT, total bilirubin, direct bilirubin, LDH, cholesterol, high-density lipoprotein [HDL], cholesterol-HDL ratio, triglycerides, and creatine phosphokinase) were not significant.

#### *13.1.2.4 Serum Dioxin Analysis of 1987 Follow-up Study Summary Results*

The 1987 serum dioxin analyses did not show a significant association with any of the verified historical liver disorder variables. The analyses of the laboratory variables detected significant associations between dioxin (current and estimated initial) and lipid-related health indices such as cholesterol, HDL cholesterol, the cholesterol-HDL ratio, and triglycerides. These findings were consistent with significant associations seen for fat-related variables in other clinical assessments, such as the body fat results in the general health assessment and the diabetes and glucose results noted in the endocrine assessment, and may represent a dioxin mediated alteration of biochemical processes.

#### *13.1.2.5 1992 Follow-up Study Summary Results*

The gastrointestinal assessment found isolated significant differences between Ranch Hands and Comparisons, but overall, the health of the two groups did not differ substantially. The serum dioxin analyses indicated that estimated initial dioxin generally was not associated with historical liver disorders

or current laboratory measurements. The analyses did reveal that current dioxin levels were often highly associated with lipid-related health indices, such as cholesterol, HDL cholesterol, the cholesterol-HDL ratio, and triglycerides, as well as with some of the hepatic enzymes (ALT and GGT) and proteins. These seemingly discordant results may have been explained in part because the initial dioxin analyses adjusted for differential half-life elimination related to body fat, while no adjustment was made in the analyses of current dioxin. These significant findings may have been the result of a subclinical dioxin effect on lipid metabolism.

### 13.1.3 Parameters for the 1997 Gastrointestinal Assessment

#### *13.1.3.1 Dependent Variables*

Questionnaire, physical examination, and laboratory data were used in the gastrointestinal assessment. The questionnaire data were organized by International Classification of Diseases, 9<sup>th</sup> Revision, Clinical Modification (ICD-9-CM) medical coding categories.

##### *13.1.3.1.1 Medical Records Data*

During the 1997 health interview, each study participant was asked about the occurrence of hepatitis, jaundice, cirrhosis, enlarged liver, and other liver conditions. This self-reported information was elicited in the questionnaire and combined with information from the baseline, 1985, 1987, and 1992 follow-up examinations and verified by a medical records review. The verified results were grouped into eight categories of disorders for analysis: uncharacterized hepatitis (non-A, non-B, non-C, and non-D), jaundice (unspecified, not of the newborn), acute necrosis of the liver, chronic liver disease and cirrhosis (alcohol-related and non-alcohol-related cirrhosis were analyzed separately), liver abscess and sequelae of chronic liver disease, enlarged liver (hepatomegaly), and other disorders of the liver. The purpose of the uncharacterized hepatitis (non-A, non-B, non-C, and non-D) category was to define a category that was neither clearly A nor B nor C nor D, so that liver disease misdiagnosed as "viral hepatitis" could be detected. This approach to historical hepatitis created a group of cases that could have been chemically induced. The following ICD-9-CM codes were used for these disorders: uncharacterized hepatitis (ICD-9-CM codes 070.49, 070.59, 070.6, 070.9, 571.40, 571.41, 571.49, and 573.3), jaundice (ICD-9-CM code 782.4), acute necrosis of the liver (ICD-9-CM code 570), alcohol-related chronic liver disease and cirrhosis (ICD-9-CM codes 571.0–571.3), non-alcohol-related chronic liver disease and cirrhosis (ICD-9-CM codes 571.40–571.9), liver abscess and sequelae of chronic liver disease (ICD-9-CM codes 572.0–572.4, 572.8), enlarged liver (ICD-9-CM code 789.1), and other disorders of the liver (ICD-9-CM codes 573.0–573.9, 790.4, 790.5, and 794.8).

For each condition, participants with a pre-Southeast Asia (SEA) diagnosis were excluded from the analysis. Also, the analysis of alcohol-related chronic liver disease and cirrhosis excluded participants with zero lifetime alcohol history because nondrinkers were not at risk for alcohol-related liver disease.

##### *13.1.3.1.2 Physical Examination Data*

One variable from the 1997 physical examination, current hepatomegaly, was analyzed in the gastrointestinal assessment. This variable was coded as "yes" or "no." Participants whose blood contained hepatitis B surface antigen or hepatitis C antibodies were excluded from the analysis of current hepatomegaly to account for the effects of these viruses on chronic hepatic disease.

### 13.1.3.1.3 Laboratory Examination Data

The 1997 examination emphasized the evaluation of laboratory data through the analysis of 29 measurements. These laboratory variables were AST (U/l), ALT (U/l), GGT (U/l), alkaline phosphatase (U/l), total bilirubin (mg/dl), direct bilirubin (mg/dl), LDH (U/l), cholesterol (mg/dl), HDL (mg/dl), cholesterol-HDL ratio, triglycerides (mg/dl), creatine phosphokinase (U/l), serum amylase (U/l), antibodies for hepatitis A, serological evidence of prior hepatitis B infection (positive hepatitis B core antibody), current hepatitis B (positive hepatitis B surface antigen), antibodies for hepatitis C, antibodies for hepatitis D, stool hemocult, and 10 components (in mg/dl) in a protein profile (prealbumin, albumin,  $\alpha$ -1-acid glycoprotein,  $\alpha$ -1-antitrypsin,  $\alpha$ -2-macroglobulin, apolipoprotein B, C3 complement, C4 complement, haptoglobin, and transferrin). IgA, IgG, and IgM were also part of this profile, but they were analyzed in the immunologic assessment (see Chapter 17).

All assays for the 1997 gastrointestinal assessment were performed by Scripps Clinic. Dade RxL<sup>®</sup> equipment was used to quantify AST, ALT, GGT, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, cholesterol, HDL, triglycerides, creatine phosphokinase, serum amylase, and albumin. The Beckman Array Protein System<sup>®</sup> quantified all components of the protein profile except albumin.

Abbott Commander<sup>®</sup> equipment was used to determine the presence or absence of antibodies of hepatitis A, serological evidence of prior hepatitis B infection, current hepatitis B, and antibodies of hepatitis C. Abbott Quantum<sup>®</sup> equipment was used to determine the presence or absence of hepatitis D antibodies. Hepatitis D testing was performed only on participants who showed serological evidence of prior hepatitis B infection or current hepatitis B, as determined by a positive hepatitis B surface antigen.

All laboratory variables were analyzed in both continuous and discrete forms except for direct bilirubin, antibodies for hepatitis A, serological evidence of present or prior hepatitis B infection, current hepatitis B, antibodies for hepatitis C, antibodies for hepatitis D, and stool hemocult, which were analyzed only in discrete form. Direct bilirubin was analyzed only in its discrete form because there were few distinct measurements, precluding a meaningful continuous analysis.

Participants whose blood contained hepatitis B surface antigen, hepatitis C antibodies, or hepatitis D antibodies were excluded from the analysis of all laboratory variables except antibodies for hepatitis A, serological evidence of prior hepatitis B infection, current hepatitis B, antibodies for hepatitis C, and antibodies for hepatitis D. Participants with body temperatures greater than or equal to 100° Fahrenheit also were excluded from the analysis of these variables. For the five hepatitis variables, no participants were excluded. Attempts were made to determine, from a medical records review, which occurrences of the types of hepatitis described above were pre-SEA, but the date of hepatitis onset was not available for the majority of participants. Consequently, all occurrences of hepatitis are included in these variables.

### 13.1.3.2 Covariates

Statistical analyses of all medical records variables were adjusted for age, race, military occupation, lifetime alcohol history, lifetime industrial chemical exposure, and lifetime degreasing chemical exposure.

Statistical analyses of the physical examination variable and all of the laboratory variables except alkaline phosphatase and  $\alpha$ -1-antitrypsin were adjusted for age, race, military occupation, current alcohol use, lifetime alcohol history, lifetime industrial chemical exposure, and lifetime industrial chemical exposure. Wine consumption showed a strong negative association with alkaline phosphatase in the 1985, 1987, and 1992 follow-up examinations. The negative association persisted in the 1992 and 1997 follow-up examination data; therefore, current wine consumption and lifetime wine history replaced current alcohol use and lifetime alcohol history as covariates in the adjusted analyses of alkaline phosphatase. Current

wine consumption also replaced current alcohol use in the adjusted analysis of  $\alpha$ -1-antitrypsin based on covariate associations in the 1997 follow-up examination data, which showed that  $\alpha$ -1-antitrypsin was highly associated with current wine consumption but not associated with current alcohol use.

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

The participants' lifetime exposures through 1992 to degreasing and industrial chemicals were updated with information reported in the 1997 questionnaire.

Age, current alcohol use (or wine consumption), and lifetime alcohol (or wine) history were treated as continuous variables wherever possible for all adjusted analyses. Degreasing chemical exposure and industrial chemical exposure were categorized as "yes" or "no" for all analyses.

#### 13.1.4 Statistical Methods

Table 13-1 summarizes the statistical analysis performed for the gastrointestinal assessment. The first part of this table lists the dependent variables analyzed, source of the data, form of the data (discrete or continuous), cutpoints, covariates, and statistical methods. The second part of this table provides a further description of the covariates examined. A covariate was used in its continuous form whenever possible for all adjusted analyses; if the covariate was inherently discrete (e.g., military occupation), or if a categorized form was needed to develop measures of association with the dependent variables, the covariate was categorized as shown in Table 13-1.

Cutpoints for cholesterol are age-dependent. Consequently, normal and abnormal levels were constructed according to a participant's laboratory value and age at the physical examination. The age-specific cutpoints are listed in Table 13-1, and the reference ages for these cutpoints are given in parentheses following the cutpoints.

**Table 13-1. Statistical Analysis for the Gastrointestinal Assessment**

#### Dependent Variables

| Variable (Units)          | Data Source | Data Form | Cutpoints | Covariates <sup>a</sup> | Exclusions <sup>b</sup> | Statistical Analysis and Methods |
|---------------------------|-------------|-----------|-----------|-------------------------|-------------------------|----------------------------------|
| Uncharacterized Hepatitis | MR-V        | D         | Yes<br>No | (1)                     | (a)                     | U:LR<br>A:LR                     |
| Jaundice (Unspecified)    | MR-V        | D         | Yes<br>No | (1)                     | (a)                     | U:LR,CS<br>A:LR                  |

**Table 13-1. Statistical Analysis for the Gastrointestinal Assessment (Continued)**

| Variable (Units)                                          | Data Source | Data Form | Cutpoints                                                                                    | Covariates <sup>a</sup> | Exclusions <sup>b</sup> | Statistical Analysis and Methods |
|-----------------------------------------------------------|-------------|-----------|----------------------------------------------------------------------------------------------|-------------------------|-------------------------|----------------------------------|
| Acute Necrosis of the Liver                               | MR-V        | D         | Yes<br>No                                                                                    | (1)                     | (a)                     | --                               |
| Chronic Liver Disease and Cirrhosis (Alcohol-related)     | MR-V        | D         | Yes<br>No                                                                                    | (1)                     | (b)                     | U:LR<br>A:LR                     |
| Chronic Liver Disease and Cirrhosis (Non-alcohol-related) | MR-V        | D         | Yes<br>No                                                                                    | (1)                     | (a)                     | U:LR<br>A:LR                     |
| Liver Abscess and Sequelae of Chronic Liver Disease       | MR-V        | D         | Yes<br>No                                                                                    | (1)                     | (a)                     | U:LR,CS<br>A:LR                  |
| Enlarged Liver (Hepatomegaly)                             | MR-V        | D         | Yes<br>No                                                                                    | (1)                     | (a)                     | U:LR<br>A:LR                     |
| Other Disorders of the Liver                              | MR-V        | D         | Yes<br>No                                                                                    | (1)                     | (a)                     | U:LR<br>A:LR                     |
| Current Hepatomegaly                                      | PE          | D         | Yes<br>No                                                                                    | (2)                     | (c)                     | U:LR,CS<br>A:LR                  |
| AST (U/l)                                                 | LAB         | D/C       | High: >37<br>Normal: ≤37                                                                     | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM<br>L:LR,GLM |
| ALT (U/l)                                                 | LAB         | D/C       | High: >65<br>Normal: ≤65                                                                     | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM<br>L:LR,GLM |
| GGT (U/l)                                                 | LAB         | D/C       | High: >85<br>Normal: ≤85                                                                     | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM<br>L:LR,GLM |
| Alkaline Phosphatase (U/l)                                | LAB         | D/C       | High: >136<br>Normal: ≤136                                                                   | (3)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Total Bilirubin (mg/dl)                                   | LAB         | D/C       | High: >1.0<br>Normal: ≤1.0                                                                   | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Direct Bilirubin (mg/dl)                                  | LAB         | D         | High: >0.3<br>Normal: ≤0.3                                                                   | (2)                     | (d)                     | U:LR,CS<br>A:LR                  |
| Lactic Dehydrogenase (LDH) (U/l)                          | LAB         | D/C       | High: >190<br>Normal: ≤190                                                                   | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Cholesterol (mg/dl)                                       | LAB         | D/C       | High:<br>>260 (Age 45-49)<br>>250 (Age ≥50)<br>Normal:<br>≤260 (Age 45-49)<br>≤250 (Age ≥50) | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM<br>L:LR,GLM |
| HDL Cholesterol (mg/dl)                                   | LAB         | D/C       | Low: <32<br>Normal: ≥32                                                                      | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM<br>L:LR,GLM |
| Cholesterol-HDL Ratio                                     | LAB         | D/C       | High: >5<br>Normal: ≤5                                                                       | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM<br>L:LR,GLM |

**Table 13-1. Statistical Analysis for the Gastrointestinal Assessment (Continued)**

| Variable (Units)                                    | Data Source | Data Form | Cutpoints                                                  | Covariates <sup>a</sup> | Exclusions <sup>b</sup> | Statistical Analysis and Methods |
|-----------------------------------------------------|-------------|-----------|------------------------------------------------------------|-------------------------|-------------------------|----------------------------------|
| Triglycerides (mg/dl)                               | LAB         | D/C       | High: >200<br>Normal: ≤200                                 | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM<br>L:LR,GLM |
| Creatine Phosphokinase (U/l)                        | LAB         | D/C       | High: >232<br>Normal: ≤232                                 | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Serum Amylase (U/l)                                 | LAB         | D/C       | High: >115<br>Normal: ≤115                                 | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Antibodies for Hepatitis A                          | LAB         | D         | Yes<br>No                                                  | (2)                     | None                    | U:LR<br>A:LR                     |
| Serological Evidence of Prior Hepatitis B Infection | LAB         | D         | Yes<br>No                                                  | (2)                     | (e)                     | U:LR<br>A:LR                     |
| Current Hepatitis B                                 | LAB         | D         | Yes<br>No                                                  | (2)                     | None                    | U:LR,CS<br>A:LR                  |
| Antibodies for Hepatitis C                          | LAB         | D         | Yes<br>No                                                  | (2)                     | None                    | U:LR<br>A:LR                     |
| Antibodies for Hepatitis D                          | LAB         | D         | Yes<br>No                                                  | (2)                     | None                    | --                               |
| Stool Hemocult                                      | LAB         | D         | Yes<br>No                                                  | (2)                     | (d)                     | U:LR<br>A:LR                     |
| Protein Profile: Prealbumin (mg/dl)                 | LAB         | D/C       | Low: <18<br>Normal: ≥18                                    | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Protein Profile: Albumin (mg/dl)                    | LAB         | D/C       | Low: <3,350<br>Normal: ≥3,350                              | (2)                     | (d)                     | U:LR,CS,GLM<br>A:LR,GLM          |
| Protein Profile: α-1-Acid Glycoprotein (mg/dl)      | LAB         | D/C       | High: >125<br>Normal: ≤125                                 | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Protein Profile: α-1-Antitrypsin (mg/dl)            | LAB         | D/C       | Abnormal Low: <93<br>Normal: 93-224<br>Abnormal High: >224 | (4)                     | (d)                     | U:PR,CS,GLM<br>A:PR,GLM          |
| Protein Profile: α-2-Macroglobulin (mg/dl)          | LAB         | D/C       | High: >293<br>Normal: ≤293                                 | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Protein Profile: Apolipoprotein B (mg/dl)           | LAB         | D/C       | High: >109<br>Normal: ≤109                                 | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Protein Profile: C3 Complement (mg/dl)              | LAB         | D/C       | Low: <85<br>Normal: ≥85                                    | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Protein Profile: C4 Complement (mg/dl)              | LAB         | D/C       | Low: <12<br>Normal: ≥12                                    | (2)                     | (d)                     | U:LR,CS,GLM<br>A:LR,GLM          |
| Protein Profile: Haptoglobin (mg/dl)                | LAB         | D/C       | High: >163<br>Normal: ≤163                                 | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |
| Protein Profile: Transferrin (mg/dl)                | LAB         | D/C       | Low: <212<br>Normal: ≥212                                  | (2)                     | (d)                     | U:LR,GLM<br>A:LR,GLM             |

**Table 13-1. Statistical Analysis for the Gastrointestinal Assessment (Continued)**

<sup>a</sup>Covariates:

- (1): age, race, military occupation, lifetime alcohol history, industrial chemical exposure, degreasing chemical exposure.
- (2): age, race, military occupation, current alcohol use, lifetime alcohol history, industrial chemical exposure, degreasing chemical exposure.
- (3): age, race, military occupation, current wine consumption, lifetime wine history, industrial chemical exposure, degreasing chemical exposure.
- (4): age, race, military occupation, current wine consumption, lifetime alcohol history, industrial chemical exposure, degreasing chemical exposure.

<sup>b</sup>Exclusions:

- (a): participants with a pre-SEA history of the disorder.
- (b): participants with a pre-SEA history of the disorder, participants with no lifetime alcohol history.
- (c): participants whose blood contained hepatitis B surface antigen, hepatitis C antibodies, or hepatitis D antibodies.
- (d): participants whose blood contained hepatitis B surface antigen, hepatitis C antibodies, or hepatitis D antibodies, participants with body temperatures greater than or equal to 100° Fahrenheit.
- (e): participants who had received the hepatitis B vaccine.

**Covariates**

| Variable (Units)                              | Data Source | Data Form | Cutpoints                                        |
|-----------------------------------------------|-------------|-----------|--------------------------------------------------|
| Age (years)                                   | MIL         | D/C       | Born ≥1942<br>Born <1942                         |
| Race                                          | MIL         | D         | Black<br>Non-Black                               |
| Occupation                                    | MIL         | D         | Officer<br>Enlisted Flyer<br>Enlisted Groundcrew |
| Current Alcohol Use (drinks/day)              | Q-SR        | D/C       | 0-1<br>>1-4<br>>4                                |
| Lifetime Alcohol History (drink-years)        | Q-SR        | D/C       | 0<br>>0-40<br>>40                                |
| Current Wine Consumption (drinks of wine/day) | Q-SR        | D/C       | 0<br>>0                                          |
| Lifetime Wine History (drink-years of wine)   | Q-SR        | D/C       | 0<br>>0                                          |
| Industrial Chemical Exposure                  | Q-SR        | D         | Yes<br>No                                        |
| Degreasing Chemical Exposure                  | Q-SR        | D         | Yes<br>No                                        |

**Abbreviations**

Data Source: LAB: 1997 laboratory results  
MIL: Air Force military records  
MR-V: Medical records (verified)  
PE: 1997 physical examination  
Q-SR: Health questionnaires (self-reported)

**Table 13-1. Statistical Analysis for the Gastrointestinal Assessment (Continued)**

|                       |                                                                                                                                             |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Data Form:            | D: Discrete analysis only                                                                                                                   |
|                       | D/C: Discrete and continuous analysis for dependent variables; appropriate form for analysis (either discrete or continuous) for covariates |
| Statistical Analysis: | U: Unadjusted analysis                                                                                                                      |
|                       | A: Adjusted analysis                                                                                                                        |
|                       | L: Longitudinal analysis                                                                                                                    |
| Statistical Methods:  | CS: Chi-square contingency table analysis (continuity-adjusted)                                                                             |
|                       | GLM: General linear models analysis                                                                                                         |
|                       | LR: Logistic regression analysis                                                                                                            |
|                       | PR: Polytomous logistic regression analysis                                                                                                 |

Table 13-2 provides a summary of the number of participants with missing dependent variable and covariate data. In addition, the number of participants excluded because of medical conditions is given.

**Table 13-2. Number of Participants Excluded or with Missing Data for the Gastrointestinal Assessment**

| Variable                                                                        | Variable Use | Group      |            | Dioxin (Ranch Hands Only) |      | Categorized Dioxin |            |
|---------------------------------------------------------------------------------|--------------|------------|------------|---------------------------|------|--------------------|------------|
|                                                                                 |              | Ranch Hand | Comparison | Initial                   | 1987 | Ranch Hand         | Comparison |
| Lactic Dehydrogenase                                                            | DEP          | 0          | 2          | 0                         | 0    | 0                  | 2          |
| HDL                                                                             | DEP          | 1          | 1          | 1                         | 1    | 1                  | 1          |
| Cholesterol-HDL Ratio                                                           | DEP          | 1          | 1          | 1                         | 1    | 1                  | 1          |
| Triglycerides                                                                   | DEP          | 1          | 0          | 0                         | 1    | 1                  | 0          |
| Antibodies for Hepatitis A                                                      | DEP          | 0          | 1          | 0                         | 0    | 0                  | 1          |
| Serological Evidence of Prior Hepatitis B Infection                             | DEP          | 0          | 1          | 0                         | 0    | 0                  | 1          |
| Stool Hemocult                                                                  | DEP          | 27         | 35         | 13                        | 25   | 25                 | 32         |
| Current Alcohol Use                                                             | COV          | 1          | 0          | 0                         | 1    | 1                  | 0          |
| Lifetime Alcohol History                                                        | COV          | 6          | 2          | 3                         | 6    | 6                  | 1          |
| Current Wine Consumption                                                        | COV          | 1          | 0          | 0                         | 1    | 1                  | 0          |
| Lifetime Wine History                                                           | COV          | 4          | 2          | 2                         | 4    | 4                  | 1          |
| Pre-SEA Jaundice                                                                | EXC          | 24         | 32         | 13                        | 24   | 24                 | 31         |
| Pre-SEA Chronic Liver Disease and Cirrhosis (Alcohol-related)                   | EXC          | 1          | 4          | 1                         | 1    | 1                  | 4          |
| No Lifetime Alcohol History                                                     | EXC          | 54         | 64         | 34                        | 54   | 54                 | 62         |
| Pre-SEA Chronic Liver Disease and Cirrhosis (Non-alcohol-related)               | EXC          | 0          | 1          | 0                         | 0    | 0                  | 1          |
| Pre-SEA Enlarged Liver                                                          | EXC          | 1          | 2          | 1                         | 1    | 1                  | 2          |
| Pre-SEA Other Liver Disorders                                                   | EXC          | 4          | 11         | 1                         | 4    | 4                  | 11         |
| Body Temperature $\geq 100^{\circ}$ Fahrenheit at the Time of the Physical Exam | EXC          | 1          | 0          | 1                         | 1    | 1                  | 0          |
| Hepatitis B Surface Antigen (Current Hepatitis B)                               | EXC          | 1          | 2          | 1                         | 1    | 1                  | 2          |

**Table 13-2. Number of Participants Excluded or with Missing Data for the Gastrointestinal Assessment (Continued)**

| Variable                   | Variable Use | Group      |            | Dioxin<br>(Ranch Hands Only) |      | Categorized Dioxin |            |
|----------------------------|--------------|------------|------------|------------------------------|------|--------------------|------------|
|                            |              | Ranch Hand | Comparison | Initial                      | 1987 | Ranch Hand         | Comparison |
| Antibodies for Hepatitis C | EXC          | 9          | 18         | 4                            | 9    | 9                  | 17         |
| Antibodies for Hepatitis D | EXC          | 1          | 0          | 1                            | 1    | 1                  | 0          |
| Vaccinated for Hepatitis B | EXC          | 1          | 1          | 1                            | 1    | 1                  | 1          |

Note: DEP = Dependent variable.

COV = Covariate.

EXC = Exclusion.

870 Ranch Hands and 1,251 Comparisons.

482 Ranch Hands for initial dioxin; 863 Ranch Hands for 1987 dioxin.

863 Ranch Hands and 1,213 Comparisons for categorized dioxin.

#### 13.1.4.1 Longitudinal Analysis

The longitudinal analysis of the gastrointestinal assessment examined seven laboratory variables (AST, ALT, GGT, cholesterol, HDL cholesterol, the cholesterol-HDL ratio, and triglycerides). Each variable was analyzed in both its continuous and discrete forms. These longitudinal analyses were used to assess any relation between herbicide exposure or dioxin levels and hepatic changes across time.

## 13.2 RESULTS

### 13.2.1 Dependent Variable-Covariate Associations

Covariate tests of association were performed to examine the relation between the covariates used in the adjusted analyses and the dependent variables. These associations are pairwise between the dependent variable and the covariate and are not adjusted for any other covariates. Appendix Table F-5 provides summary results of these analyses, including correlation coefficients ( $r$ ), percents abnormal, means, and  $p$ -values to test the statistical significance of the associations. Statistically significant ( $p \leq 0.05$ ) associations are discussed below.

#### 13.2.1.1 Medical Records Variables

The association between a history of uncharacterized hepatitis and lifetime alcohol consumption was significant ( $p=0.010$ ). Uncharacterized hepatitis decreased as lifetime alcohol consumption increased.

Tests of covariate association showed race ( $p=0.025$ ), lifetime alcohol history ( $p=0.001$ ), and industrial chemical exposure ( $p=0.024$ ) to be significantly associated with alcohol-related chronic liver disease. Black participants had a higher prevalence of alcohol-related chronic liver disease than non-Blacks (9.5% vs. 4.5%). The percentage of participants with chronic liver disease increased as lifetime alcohol consumption increased. Participants who reported exposure to industrial chemicals had a higher percentage of alcohol-related chronic liver disease (5.6%) than participants who did not report exposure (3.3%).

Non-alcohol-related chronic liver disease was significantly associated with lifetime alcohol history ( $p=0.011$ ). Moderate drinkers (in terms of drink-years) had the highest percentage of non-alcohol-related chronic liver disease (1.8%), followed by nondrinkers (1.7%) and heavier drinkers (0.2%).

The percentage of participants with enlarged livers increased with age ( $p=0.038$ ) and lifetime alcohol history ( $p=0.001$ ).

Other liver disorders were significantly associated with race ( $p=0.001$ ) and lifetime alcohol history ( $p=0.043$ ). The prevalence of other liver disorders was greater for Blacks (43.0%) than for non-Blacks (25.6%). The percentage of participants with a history of other liver disorders increased as drinking increased.

#### *13.2.1.2 Laboratory Examination Variables*

AST in its continuous form increased with current alcohol use ( $p<0.001$ ) and lifetime alcohol history ( $p=0.002$ ). Dichotomized AST showed an increase in the percentage of high AST levels as current alcohol use increased ( $p=0.001$ ).

ALT in its discrete form was significantly associated with age ( $p<0.001$ ) and occupation ( $p=0.009$ ). Younger participants had a larger percentage of high ALT values than did older participants (10.0% vs. 5.4%). Enlisted flyers had the highest percentage of high ALT values (10.1%), followed by enlisted groundcrew (8.2%), then officers (5.4%). ALT in its continuous form significantly decreased with age ( $p<0.001$ ) and increased with current alcohol use ( $p=0.009$ ).

For GGT in its continuous form, tests of covariate association were significant for age ( $p<0.001$ ), race ( $p=0.012$ ), occupation ( $p=0.026$ ), current alcohol use ( $p<0.001$ ), and lifetime alcohol history ( $p<0.001$ ). Levels of GGT decreased with age. Black participants showed significantly higher mean GGT levels than non-Blacks (48.65 U/l versus 42.70 U/l). Enlisted flyers had the highest mean GGT levels (44.91 U/l), followed by the enlisted groundcrew (43.87 U/l) and officers (41.38 U/l). GGT levels increased with current alcohol use and lifetime alcohol history. Tests of covariate association for GGT in its discrete form showed similar results, except that race was not significantly associated with the discrete form of GGT.

Alkaline phosphatase in its continuous form was significantly associated with occupation ( $p<0.001$ ), current wine consumption ( $p<0.001$ ), and lifetime wine history ( $p<0.001$ ). Mean alkaline phosphatase levels decreased with current wine consumption and lifetime wine history. Enlisted flyers had the highest mean alkaline phosphatase level (83.60 U/l), followed by enlisted groundcrew (82.29 U/l) and officers (77.43 U/l).

Total bilirubin in its continuous form increased with age ( $p=0.005$ ) and current alcohol use ( $p<0.001$ ). Occupation ( $p=0.001$ ) and degreasing chemical exposure ( $p=0.020$ ) also were associated significantly with total bilirubin in its continuous form. Officers showed the highest mean total bilirubin level (0.544 mg/dl), followed by enlisted flyers (0.502 mg/dl) and enlisted groundcrew (0.504 mg/dl). Participants who reported exposure to degreasing chemicals had a higher mean total bilirubin level (0.536 mg/dl) than did those who did not report exposure (0.510 mg/dl). Results of the test for discretized total bilirubin revealed a significant association with current alcohol use ( $p=0.023$ ). Participants who were currently moderate drinkers (in terms of drinks per day) had the lowest prevalence of high total bilirubin values (5.4%), followed by those who were lighter drinkers (5.7%) and those who were heavier drinkers (15.2%). The percentage of participants with high direct bilirubin levels increased with current alcohol use ( $p=0.004$ ) and lifetime drinking history ( $p=0.013$ ).

Lactic dehydrogenase in its continuous form increased with age ( $p<0.001$ ).

Tests of covariate association for cholesterol in its continuous form showed a significant association with age ( $p=0.025$ ), occupation ( $p=0.004$ ), and current alcohol use ( $p<0.001$ ). Cholesterol levels decreased with age and increased with current alcohol use. Enlisted flyers had the highest mean cholesterol levels (215.7 mg/dl), followed by the enlisted groundcrew (212.9 mg/dl) and officers (208.5 mg/dl).

Cholesterol in its discretized form showed significant associations with current alcohol use ( $p=0.009$ ) and lifetime alcohol history ( $p=0.047$ ). Participants who were moderate drinkers had the highest prevalence of high cholesterol levels (19.8%), followed by heavier drinkers (19.6%) and participants who were lighter drinkers (13.7%). The percentage of participants with high cholesterol levels increased with lifetime alcohol history.

HDL cholesterol in its continuous form increased with current alcohol use ( $p<0.001$ ) and lifetime alcohol history ( $p<0.001$ ). Race ( $p=0.002$ ), occupation ( $p<0.001$ ), industrial chemical exposure ( $p=0.005$ ), and degreasing chemical exposure ( $p=0.001$ ) also were associated significantly with HDL cholesterol. Black participants had higher mean HDL cholesterol levels than non-Blacks (48.17 mg/dl vs. 44.70 mg/dl). Officers had higher mean HDL cholesterol levels (46.67 mg/dl), followed by enlisted flyers (44.24 mg/dl) and enlisted groundcrew (43.59 mg/dl). Participants who reported exposure to industrial chemicals had lower mean HDL cholesterol levels (44.33 mg/dl) than those who did not report exposure (45.81 mg/dl). Similarly, participants who reported exposure to degreasing chemicals had lower mean HDL cholesterol levels (44.25 mg/dl) than those who did not report exposure (46.07 mg/dl).

Tests of covariate association for HDL cholesterol in its discrete form showed similar results. Significant covariates were occupation ( $p=0.002$ ), current alcohol use ( $p=0.001$ ), lifetime alcohol history ( $p=0.001$ ), industrial chemical exposure ( $p=0.028$ ), and degreasing chemical exposure ( $p=0.023$ ). Race was not significantly associated with HDL cholesterol in its discrete form. Enlisted flyers had the highest percentage of low HDL cholesterol levels (10.2%), followed by the enlisted groundcrew (9.1%) and officers (5.2%). Participants who were currently light drinkers had the highest percentage of low HDL cholesterol levels (9.0%), followed by heavier drinkers (4.3%) and moderate drinkers (2.4%). The prevalence of low HDL cholesterol levels decreased as lifetime alcohol consumption increased. In each of the analyses of industrial chemical exposure and degreasing chemical exposure, participants who reported exposure had a higher percentage of low HDL cholesterol levels.

The cholesterol-HDL ratio in its continuous form decreased with age ( $p=0.003$ ), current alcohol use ( $p<0.001$ ), and lifetime alcohol history ( $p<0.001$ ). Significant associations also were found with race ( $p=0.011$ ), occupation ( $p<0.001$ ), industrial chemical exposure ( $p<0.001$ ), and degreasing chemical exposure ( $p<0.001$ ). Non-Blacks had a higher mean cholesterol-HDL ratio than Blacks (4.69 vs. 4.39). Enlisted groundcrew had the highest mean cholesterol-HDL ratio (4.85), followed by enlisted flyers (4.84) and officers (4.43). For both industrial chemical exposure and degreasing chemical exposure covariates, participants who reported exposure had higher mean cholesterol-HDL ratios.

The tests of covariate association for the cholesterol-HDL ratio in its discrete form showed similar results. Younger participants had a higher prevalence of high cholesterol-HDL ratios than did the older participants (44.5% vs. 38.7%,  $p=0.008$ ). Non-Blacks had a larger percentage of high cholesterol-HDL ratios than Blacks (42.0% vs. 28.3%,  $p=0.004$ ). Occupation was significantly associated with the discrete form of the cholesterol-HDL ratio ( $p=0.001$ ). Enlisted groundcrew had the highest prevalence of low cholesterol-HDL ratios (48.2%), followed by enlisted flyers (43.4%) and officers (32.6%). The percentage of participants with high cholesterol-HDL ratios decreased with increased current alcohol use ( $p=0.001$ ) and increased lifetime alcohol history ( $p=0.001$ ). For both industrial chemical exposure and degreasing chemical exposure covariates, participants who reported exposure had higher percentages of high cholesterol-HDL ratios ( $p=0.001$  for both covariates).

Triglycerides in its continuous form significantly decreased with age ( $p=0.001$ ). Significant associations with race ( $p<0.001$ ), occupation ( $p<0.001$ ), industrial chemical exposure ( $p=0.013$ ), and degreasing chemical exposure ( $p=0.002$ ) also were revealed. Non-Black participants had a higher mean triglycerides level than Blacks (123.5 mg/dl vs. 93.0 mg/dl). Enlisted flyers had the highest mean triglycerides level (131.3 mg/dl), followed by enlisted groundcrew (126.1 mg/dl) and officers (113.0 mg/dl). Participants who reported exposure to industrial chemicals had higher mean triglyceride levels than those who did not report exposure (124.9 mg/dl vs. 116.4 mg/dl). Similarly, participants who reported exposure to degreasing chemicals had higher mean triglyceride levels (125.6 mg/dl) than those who did not report exposure (114.7 mg/dl).

The tests of covariate association for triglycerides in its discrete form showed significant associations with age ( $p=0.003$ ), race ( $p=0.001$ ), occupation ( $p=0.002$ ), industrial chemical exposure ( $p=0.035$ ), and degreasing chemical exposure ( $p=0.012$ ). The prevalence of high triglyceride levels was higher among the younger participants than the older participants (24.0% vs. 18.6%). Non-Blacks had a larger percentage of high triglycerides than Blacks (21.8% vs. 6.7%). Enlisted flyers had the highest percentage of high triglyceride levels (24.2%), followed by the enlisted groundcrew (23.2%) and officers (17.1%). For both industrial chemical exposure and degreasing chemical exposure covariates, participants who reported exposure had higher percentages of high triglyceride levels.

Creatine phosphokinase in its continuous form significantly decreased with age ( $p<0.001$ ) and current alcohol use ( $p=0.013$ ). Also significant were race ( $p<0.001$ ) and occupation ( $p=0.038$ ). Black participants had a higher mean creatine phosphokinase level than non-Blacks (195.9 U/l vs. 102.0 U/l). Enlisted groundcrew had the highest mean creatine phosphokinase levels (109.2 U/l), followed by officers (104.9 U/l), then enlisted flyers (99.2 U/l).

Tests of covariate association for creatine phosphokinase in its discrete form showed a significant association with age ( $p=0.006$ ), race ( $p=0.001$ ), and current alcohol use ( $p=0.018$ ). Younger participants had a larger percentage of high creatine phosphokinase values than did the older participants (11.0% vs. 7.4%). Black participants had a larger percentage of high creatine phosphokinase values than non-Blacks (34.2% vs. 7.1%). Participants who were currently heavier drinkers had the highest prevalence of high creatine phosphokinase values (10.9%), followed by lighter drinkers (9.7%) and moderate drinkers (5.1%).

Serum amylase in its continuous form showed significant associations with race ( $p<0.001$ ) and current alcohol use ( $p=0.001$ ). Blacks had a higher mean serum amylase level (72.71 U/l) than non-Blacks (56.04 U/l). Serum amylase levels decreased as current alcohol use increased. The discrete form of serum amylase was significantly associated with race ( $p=0.001$ ). Blacks had a larger percentage of high serum amylase values than non-Blacks (10.8% vs. 2.5%).

Tests of covariate association for the presence of antibodies for hepatitis A showed significant associations with age ( $p=0.001$ ), race ( $p=0.012$ ), occupation ( $p=0.001$ ), and lifetime alcohol history ( $p=0.001$ ). A higher percentage of the older participants had hepatitis A antibodies (40.9%) than the younger participants (23.5%). Black participants had a higher prevalence of hepatitis A antibodies than did non-Black participants (43.8% vs. 32.5%). Enlisted flyers had the highest percentage of participants with antibodies for hepatitis A (47.3%), followed by enlisted groundcrew (33.6%) and officers (27.0%). The highest percentage of positive results for hepatitis A antibodies was among nondrinkers (45.8%), followed by heavy lifetime drinkers (35.9%) and moderate lifetime drinkers (30.9%).

Evidence of prior hepatitis B infection was significantly associated with race ( $p=0.001$ ), occupation ( $p=0.001$ ), and lifetime alcohol history ( $p=0.001$ ). Black participants had a higher percentage of prior hepatitis B infections than non-Blacks (26.8% vs. 10.7%). Enlisted flyers had the highest percentage of prior hepatitis B infections (16.6%), followed by enlisted groundcrew (14.9%) and officers (6.0%). The

percentage of participants with serological evidence of prior hepatitis B infections increased with lifetime alcohol consumption.

Current hepatitis B was significantly associated with race ( $p=0.001$ ) and current alcohol use ( $p=0.002$ ). Black participants had a higher percentage of positive current hepatitis B results than did non-Black participants (1.6% vs. 0.1%). Participants who were currently heavier drinkers had the highest prevalence of current hepatitis B (2.0%), followed by lighter drinkers (0.1%) and moderate drinkers (0.0%).

The presence of hepatitis C antibodies was significantly associated with race ( $p=0.002$ ), occupation ( $p=0.024$ ), current alcohol use ( $p=0.004$ ), and industrial chemical exposure ( $p=0.022$ ). Black participants had a higher percentage of positive hepatitis C results than non-Blacks (4.7% vs. 1.1%). Enlisted groundcrew had the highest prevalence of positive results for hepatitis C antibodies (2.0%), followed by enlisted flyers (0.9%) and officers (0.6%). Participants who were currently heavier drinkers had the highest percentage of positive hepatitis C results (6.0%), followed by lighter drinkers (1.2%) and moderate drinkers (0.5%). Participants who reported exposure to industrial chemicals had a higher percentage of positive hepatitis C results than did participants who did not report exposure (1.7% vs. 0.5%).

The results of the tests of covariate association for stool hemocult revealed that age and industrial chemical exposure were statistically significant ( $p=0.006$  and  $p=0.021$ , respectively). Older participants had a higher percentage of positive stool hemocult results (5.1%) than did the younger participants (2.6%). Participants who did not report exposure to industrial chemicals had a higher prevalence of positive stool hemocult results (5.4%) than did those who reported exposure (3.2%).

Prealbumin in its continuous form significantly decreased with age ( $p<0.001$ ) and increased with current alcohol use ( $p<0.001$ ). Covariate association tests for discretized prealbumin revealed significant associations with current alcohol use ( $p=0.003$ ) and lifetime alcohol history ( $p=0.003$ ). The prevalence of low prealbumin levels increased with current alcohol use. Heavy lifetime drinkers had a higher prevalence of low prealbumin levels (2.3%), followed by nondrinkers (1.7%) and moderate lifetime drinkers (0.6%).

Albumin in its continuous form was significantly associated with age ( $p<0.001$ ) and degreasing chemical exposure ( $p=0.017$ ). Albumin was inversely associated with age, and participants who reported exposure to degreasing chemicals had a lower mean albumin level than those who did not report exposure (4,185.8 mg/dl vs. 4,222.3 mg/dl). Dichotomized albumin was only significantly associated with current alcohol use ( $p=0.047$ ). The percentage of participants with low albumin levels increased with current alcohol use.

Tests of covariate association for  $\alpha$ -1-acid glycoprotein in its continuous form showed significant associations with occupation ( $p<0.001$ ), current alcohol use ( $p<0.001$ ), and lifetime alcohol history ( $p<0.001$ ). Levels of  $\alpha$ -1-acid glycoprotein increased with current alcohol use and lifetime alcohol history. Enlisted groundcrew had the highest mean  $\alpha$ -1-acid glycoprotein level (86.34 mg/dl), followed by enlisted flyers (85.71 mg/dl) and officers (81.68 mg/dl).

The discrete form of  $\alpha$ -1-acid glycoprotein was significantly associated with current alcohol use ( $p=0.003$ ). The prevalence of high  $\alpha$ -1-acid glycoprotein values increased as current alcohol use increased.

The continuous form of  $\alpha$ -1-antitrypsin increased with age ( $p<0.001$ ) and lifetime alcohol history ( $p=0.001$ ) and decreased with current wine consumption ( $p<0.001$ ). Race ( $p=0.006$ ), occupation ( $p<0.001$ ), industrial chemical exposure ( $p=0.001$ ), and degreasing chemical exposure ( $p=0.023$ ) also were significant. Non-Black participants had a higher mean  $\alpha$ -1-antitrypsin level than did Black participants (148.3 mg/dl vs. 141.8 mg/dl). Enlisted flyers had the highest mean  $\alpha$ -1-antitrypsin level

(153.0 mg/dl), followed by the enlisted groundcrew (150.2 mg/dl) and officers (143.4 mg/dl). In both industrial chemical exposure and degreasing chemical exposure, participants who reported exposure had higher mean  $\alpha$ -1-antitrypsin levels.

The trichotomous form of  $\alpha$ -1-antitrypsin was significantly associated with occupation ( $p=0.022$ ), industrial chemical exposure ( $p=0.037$ ), and current wine consumption ( $p=0.031$ ). Officers had the highest percentage of abnormally low  $\alpha$ -1-antitrypsin levels (2.3%), followed by enlisted groundcrew (0.9%) and enlisted flyers (0.6%). Enlisted flyers and enlisted groundcrew each had 0.9 percent abnormally high  $\alpha$ -1-antitrypsin values, followed by officers with 0.2 percent abnormally high  $\alpha$ -1-antitrypsin values. Participants who did not report exposure to industrial chemicals had a higher percentage of abnormally low  $\alpha$ -1-antitrypsin levels (2.1%), as well as a higher percentage of abnormally high  $\alpha$ -1-antitrypsin levels (0.9%) than participants who reported exposure to industrial chemicals (0.9 percent abnormally low and 0.5 percent abnormally high). Participants who currently drank wine had a higher percentage of abnormally low  $\alpha$ -1-antitrypsin values than those who did not drink wine (1.9% vs. 1.0%). Participants who currently did not drink wine had a higher percentage of abnormally high  $\alpha$ -1-antitrypsin values than did those who currently did drink wine (0.9% vs. 0.2%).

The continuous form of  $\alpha$ -2-macroglobulin increased with age ( $p<0.001$ ) and decreased with current alcohol use ( $p=0.031$ ). Race and occupation were associated significantly with  $\alpha$ -2-macroglobulin ( $p<0.001$  and  $p=0.013$ , respectively). Non-Black participants had a higher mean  $\alpha$ -2-macroglobulin level than did Black participants (172.2 mg/dl vs. 152.1 mg/dl). Enlisted flyers had the highest mean  $\alpha$ -2-macroglobulin level (177.2 mg/dl), followed by officers (170.8 mg/dl) and enlisted groundcrew (169.0 mg/dl).

Tests of covariate association for discretized  $\alpha$ -2-macroglobulin found significant covariate associations with age and lifetime alcohol history ( $p=0.001$  each). The prevalence of high  $\alpha$ -2-macroglobulin levels increased with age. Nondrinkers had the highest percentage of high  $\alpha$ -1-macroglobulin levels, followed by heavy drinkers and moderate lifetime drinkers (9.3%, 3.3%, and 2.9%, respectively).

In its continuous form, tests of covariate association showed apolipoprotein B levels significantly decreased with age ( $p=0.023$ ). Occupation also was associated significantly with apolipoprotein B ( $p<0.001$ ). Enlisted flyers had the highest mean apolipoprotein B level (114.3 mg/dl), followed by the enlisted groundcrew (112.4 mg/dl) and officers (108.3 mg/dl). Apolipoprotein B in its discrete form showed a significant covariate association with occupation ( $p=0.004$ ). Enlisted flyers had the highest prevalence of high apolipoprotein B values (56.1%), followed by enlisted groundcrew (53.7%) and officers (47.1%).

C3 complement in its continuous form decreased with age ( $p=0.027$ ), current alcohol use ( $p<0.001$ ), and lifetime alcohol history ( $p=0.034$ ). Race ( $p=0.002$ ), occupation ( $p<0.001$ ), industrial chemical exposure ( $p<0.001$ ), and degreasing chemical exposure ( $p<0.001$ ) also were associated significantly with C3 complement. Non-Black participants had a lower mean C3 complement level than Black participants (118.4 mg/dl vs. 124.0 mg/dl). Officers had the lowest mean C3 complement level (114.7 mg/dl), followed by enlisted flyers (120.5 mg/dl) and enlisted groundcrew (121.6 mg/dl). For each of the industrial chemical exposure and degreasing chemical exposure covariates, participants who did not report exposure had lower mean C3 complement levels.

Current alcohol use was significantly associated with C3 complement in its discrete form ( $p=0.001$ ). Participants who were currently moderate drinkers had the highest percentage of low C3 complement values (4.6%), followed by lighter drinkers (1.6%) and heavier drinkers (0.0%).

Tests of covariate association showed C4 complement in its continuous form to be significantly associated with race ( $p<0.001$ ), occupation ( $p<0.001$ ), and industrial chemical exposure ( $p=0.029$ ). Non-Black participants had a lower mean C4 complement level than Black participants (25.65 mg/dl vs. 29.00 mg/dl). Officers had the lowest mean C4 complement level (25.21 mg/dl), followed by enlisted flyers (25.95 mg/dl) and enlisted groundcrew (26.35 mg/dl). Participants who did not report exposure to industrial chemicals had a lower mean C4 complement level than those who reported exposure (25.51 mg/dl vs. 26.02 mg/dl).

C4 complement in its discrete form was significantly associated with degreasing chemical exposure ( $p=0.031$ ). Participants who did not report exposure had a higher prevalence of low C4 complement values (0.5%) than those who reported exposure (0.0%).

In its continuous form, tests of covariate association showed haptoglobin levels increased significantly with current alcohol use and lifetime alcohol history ( $p=0.013$  and  $p<0.001$ , respectively). Occupation, industrial chemical exposure, and degreasing chemical exposure also were associated significantly with haptoglobin ( $p<0.001$ ,  $p=0.013$ , and  $p=0.001$ , respectively). Enlisted flyers had the highest mean haptoglobin level (142.0 mg/dl), followed by enlisted groundcrew (136.3 mg/dl) and officers (118.7 mg/dl). In each of the industrial chemical exposure and degreasing chemical exposure covariates, participants who reported exposure had higher mean haptoglobin levels.

In its discrete form, tests of covariate association for haptoglobin showed similar results to the continuous analysis. Significant covariates were occupation ( $p=0.001$ ), current alcohol use ( $p=0.005$ ), lifetime alcohol history ( $p=0.018$ ), industrial chemical exposure ( $p=0.010$ ), and degreasing chemical exposure ( $p=0.003$ ). Enlisted flyers had the highest percentage of high haptoglobin levels (36.1%), followed by enlisted groundcrew (33.8%) and officers (22.9%). The prevalence of high haptoglobin levels increased with current alcohol use. Heavy lifetime drinkers had the largest percentage of high haptoglobin values (34.2%), followed by nondrinkers (30.5%) and moderate lifetime drinkers (27.8%). In each of the analyses of industrial chemical exposure and degreasing chemical exposure, participants who reported exposure had a larger percentage of high haptoglobin levels.

Transferrin in its continuous form significantly decreased with age ( $p=0.022$ ) and increased with current alcohol use ( $p=0.022$ ). Also significantly associated with transferrin were race ( $p<0.001$ ) and degreasing chemical exposure ( $p=0.009$ ). Black participants had a lower mean transferrin level than non-Blacks (237.8 mg/dl vs. 251.7 mg/dl). Participants who reported exposure to degreasing chemicals had a lower mean transferrin level than those who were exposed (248.2 mg/dl vs. 252.4 mg/dl).

Tests of covariate association for discretized transferrin showed age and race to be significantly associated with transferrin ( $p=0.043$  and  $p=0.001$ , respectively). Older participants had a higher prevalence of low transferrin levels than did younger participants (11.0% vs. 8.2%). Blacks had a higher percentage of low transferrin levels than non-Blacks (20.8% vs. 9.1%).

### 13.2.2 Exposure Analysis

The following section presents results of the statistical analyses of the dependent variables shown in Table 13-1. Dependent variables were derived from a medical records review and verification of self-reported gastrointestinal conditions, a 1997 physical examination determination of hepatomegaly, and numerous laboratory measurements conducted at the 1997 follow-up examination.

Four models were examined for each dependent variable given in Table 13-1. The analyses of these models are presented below. Further details on dioxin and the modeling strategy are found in Chapters 2 and 7, respectively. These analyses were performed both unadjusted and adjusted for relevant covariates. Model 1 examined the relation between the dependent variable and group (i.e., Ranch Hand or Comparison). In this model, exposure was defined as "yes" for Ranch Hands and "no" for Comparisons

without regard to the magnitude of the exposure. As an attempt to quantify exposure, three contrasts of Ranch Hands and Comparisons were performed along with the overall Ranch Hand versus Comparison contrast. These three contrasts compared Ranch Hands and Comparisons within each occupational category (i.e., officers, enlisted flyers, and enlisted groundcrew). As described in previous reports, the average levels of exposure to dioxin were highest for enlisted groundcrew, followed by enlisted flyers, then officers.

Model 2 explored the relation between the dependent variable and an extrapolated initial dioxin measure for Ranch Hands who had a 1987 dioxin measurement greater than 10 parts per trillion (ppt). If a participant did not have a 1987 dioxin level, the 1992 level was used to estimate the initial dioxin level. If a participant did not have a 1987 or a 1992 dioxin level, the 1997 level was used to estimate the initial dioxin level. A statistical adjustment for the percentage of body fat at the time of the participant's blood measurement of dioxin was included in this model to account for body-fat-related differences in elimination rate (66).

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

Model 4 examined the relation between the dependent variable and 1987 lipid-adjusted dioxin levels in all Ranch Hands with a dioxin measurement. If a participant did not have a 1987 dioxin measurement, the 1992 measurement was used to determine the dioxin level. If a participant did not have a 1987 or a 1992 dioxin measurement, the 1997 measurement was used to determine the dioxin level.

#### *13.2.2.1 Medical Records Variables*

##### *13.2.2.1.1 Uncharacterized Hepatitis*

All unadjusted and adjusted analyses of the appearance of uncharacterized hepatitis for Models 1 through 4 were nonsignificant (Table 13-3(a-h):  $p > 0.18$  for all analyses).

**Table 13-3. Analysis of Uncharacterized Hepatitis**

**(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED**

| Occupational Category | Group      | n     | Number (%)<br>Yes | Est. Relative Risk<br>(95% C.I.) | p-Value |
|-----------------------|------------|-------|-------------------|----------------------------------|---------|
| All                   | Ranch Hand | 863   | 17 (2.0)          | 1.17 (0.61,2.23)                 | 0.634   |
|                       | Comparison | 1,244 | 21 (1.7)          |                                  |         |
| Officer               | Ranch Hand | 338   | 5 (1.5)           | 1.03 (0.32,3.28)                 | 0.958   |
|                       | Comparison | 488   | 7 (1.4)           |                                  |         |
| Enlisted Flyer        | Ranch Hand | 151   | 4 (2.6)           | 1.67 (0.37,7.57)                 | 0.507   |
|                       | Comparison | 187   | 3 (1.6)           |                                  |         |
| Enlisted Groundcrew   | Ranch Hand | 374   | 8 (2.1)           | 1.11 (0.44,2.78)                 | 0.826   |
|                       | Comparison | 569   | 11 (1.9)          |                                  |         |

**(b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED**

| Occupational Category | Adjusted Relative Risk<br>(95% C.I.) | p-Value |
|-----------------------|--------------------------------------|---------|
| All                   | 1.18 (0.62,2.26)                     | 0.617   |
| Officer               | 1.05 (0.33,3.35)                     | 0.935   |
| Enlisted Flyer        | 1.62 (0.35,7.40)                     | 0.533   |
| Enlisted Groundcrew   | 1.13 (0.45,2.85)                     | 0.795   |

**(c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED**

| Initial Dioxin Category Summary Statistics |     |                   | Analysis Results for Log <sub>2</sub> (Initial Dioxin) <sup>a</sup> |         |
|--------------------------------------------|-----|-------------------|---------------------------------------------------------------------|---------|
| Initial Dioxin                             | n   | Number (%)<br>Yes | Estimated Relative Risk<br>(95% C.I.) <sup>b</sup>                  | p-Value |
| Low                                        | 158 | 3 (1.9)           | 1.10 (0.67,1.80)                                                    | 0.705   |
| Medium                                     | 161 | 3 (1.9)           |                                                                     |         |
| High                                       | 159 | 3 (1.9)           |                                                                     |         |

<sup>a</sup> Adjusted for percent body fat at the time of the blood measurement of dioxin.

<sup>b</sup> Relative risk for a twofold increase in initial dioxin.

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

**(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED**

| Analysis Results for Log <sub>2</sub> (Initial Dioxin) |                                                   |         |
|--------------------------------------------------------|---------------------------------------------------|---------|
| n                                                      | Adjusted Relative Risk<br>(95% C.I.) <sup>a</sup> | p-Value |
| 475                                                    | 1.02 (0.58,1.79)                                  | 0.936   |

<sup>a</sup> Relative risk for a twofold increase in initial dioxin.

Note: Results are not adjusted for race, industrial chemical exposure, and degreasing chemical exposure because of the sparse number of Ranch Hands with uncharacterized hepatitis.

**Table 13-3. Analysis of Uncharacterized Hepatitis (Continued)**

| <b>(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED</b> |          |                           |                                                       |                |
|---------------------------------------------------------------------------------|----------|---------------------------|-------------------------------------------------------|----------------|
| <b>Dioxin Category</b>                                                          | <b>n</b> | <b>Number (%)<br/>Yes</b> | <b>Est. Relative Risk<br/>(95% C.I.)<sup>ab</sup></b> | <b>p-Value</b> |
| Comparison                                                                      | 1,206    | 21 (1.7)                  |                                                       |                |
| Background RH                                                                   | 378      | 8 (2.1)                   | 1.27 (0.56,2.92)                                      | 0.568          |
| Low RH                                                                          | 237      | 4 (1.7)                   | 0.96 (0.33,2.82)                                      | 0.938          |
| High RH                                                                         | 241      | 5 (2.1)                   | 1.15 (0.43,3.10)                                      | 0.779          |
| Low plus High RH                                                                | 478      | 9 (1.9)                   | 1.05 (0.48,2.32)                                      | 0.902          |

<sup>a</sup> Relative risk and confidence interval relative to Comparisons.

<sup>b</sup> Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

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

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

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

| <b>(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED</b> |          |                                                          |                |
|-------------------------------------------------------------------------------|----------|----------------------------------------------------------|----------------|
| <b>Dioxin Category</b>                                                        | <b>n</b> | <b>Adjusted Relative Risk<br/>(95% C.I.)<sup>a</sup></b> | <b>p-Value</b> |
| Comparison                                                                    | 1,205    |                                                          |                |
| Background RH                                                                 | 375      | 1.39 (0.59,3.27)                                         | 0.450          |
| Low RH                                                                        | 236      | 1.00 (0.34,2.97)                                         | 0.999          |
| High RH                                                                       | 239      | 1.04 (0.38,2.89)                                         | 0.932          |
| Low plus High RH                                                              | 475      | 1.02 (0.46,2.28)                                         | 0.957          |

<sup>a</sup> Relative risk and confidence interval relative to Comparisons.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

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

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

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

| <b>(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED</b> |          |                           |                                                               |                |
|------------------------------------------------------------|----------|---------------------------|---------------------------------------------------------------|----------------|
| <b>1987 Dioxin Category Summary Statistics</b>             |          |                           | <b>Analysis Results for Log<sub>2</sub> (1987 Dioxin + 1)</b> |                |
| <b>1987<br/>Dioxin</b>                                     | <b>n</b> | <b>Number (%)<br/>Yes</b> | <b>Estimated Relative Risk<br/>(95% C.I.)<sup>a</sup></b>     | <b>p-Value</b> |
| Low                                                        | 287      | 6 (2.1)                   | 0.86 (0.61,1.21)                                              | 0.377          |
| Medium                                                     | 283      | 5 (1.8)                   |                                                               |                |
| High                                                       | 286      | 6 (2.1)                   |                                                               |                |

<sup>a</sup> Relative risk for a twofold increase in 1987 dioxin.

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

**Table 13-3. Analysis of Uncharacterized Hepatitis (Continued)**

| <b>(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED</b> |                                                   |         |
|----------------------------------------------------------|---------------------------------------------------|---------|
| Analysis Results for Log <sub>2</sub> (1987 Dioxin + 1)  |                                                   |         |
| n                                                        | Adjusted Relative Risk<br>(95% C.I.) <sup>a</sup> | p-Value |
| 850                                                      | 0.78 (0.55,1.12)                                  | 0.184   |

<sup>a</sup> Relative risk for a twofold increase in 1987 dioxin.

#### 13.2.2.1.2 Jaundice (Unspecified)

The unadjusted Model 1 analysis revealed a significant overall group difference in the percentage of individuals with jaundice (Table 13-4(a): Est. RR=0.49, p=0.025). The percentage of Ranch Hands with jaundice was 1.4 percent versus 2.9 percent of the Comparisons. After stratifying by occupation, marginally significant differences were seen between Ranch Hand and Comparison officers, as well as enlisted groundcrew (Table 13-4(a): Est. RR=0.45, p=0.091; Est. RR=0.30, p=0.057, respectively). The percentage of officers and enlisted groundcrew with jaundice was higher among the Comparisons than the Ranch Hands.

**Table 13-4. Analysis of Jaundice (Unspecified)**

| <b>(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED</b> |                   |       |                   |                                  |         |
|--------------------------------------------------------------|-------------------|-------|-------------------|----------------------------------|---------|
| Occupational Category                                        | Group             | n     | Number (%)<br>Yes | Est. Relative Risk<br>(95% C.I.) | p-Value |
| <i>All</i>                                                   | <i>Ranch Hand</i> | 846   | 12 (1.4)          | 0.49 (0.25,0.94)                 | 0.025   |
|                                                              | <i>Comparison</i> | 1,219 | 35 (2.9)          |                                  |         |
| Officer                                                      | Ranch Hand        | 329   | 6 (1.8)           | 0.45 (0.18,1.14)                 | 0.091   |
|                                                              | Comparison        | 478   | 19 (4.0)          |                                  |         |
| Enlisted Flyer                                               | Ranch Hand        | 149   | 3 (2.0)           | 3.70 (0.38,35.9)                 | 0.260   |
|                                                              | Comparison        | 181   | 1 (0.6)           |                                  |         |
| Enlisted Groundcrew                                          | Ranch Hand        | 368   | 3 (0.8)           | 0.30 (0.09,1.04)                 | 0.057   |
|                                                              | Comparison        | 560   | 15 (2.7)          |                                  |         |

  

| <b>(b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED</b> |                                      |         |
|------------------------------------------------------------|--------------------------------------|---------|
| Occupational Category                                      | Adjusted Relative Risk<br>(95% C.I.) | p-Value |
| <i>All</i>                                                 | 0.49 (0.25,0.96)                     | 0.028   |
| Officer                                                    | 0.46 (0.18,1.17)                     | 0.103   |
| Enlisted Flyer                                             | 3.47 (0.36,33.8)                     | 0.284   |
| Enlisted Groundcrew                                        | 0.29 (0.08,1.03)                     | 0.055   |

**Table 13-4. Analysis of Jaundice (Unspecified) (Continued)**

| <b>(c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED</b> |     |                   |                                                                     |         |
|---------------------------------------------------------------|-----|-------------------|---------------------------------------------------------------------|---------|
| Initial Dioxin Category Summary Statistics                    |     |                   | Analysis Results for Log <sub>2</sub> (Initial Dioxin) <sup>a</sup> |         |
| Initial Dioxin                                                | n   | Number (%)<br>Yes | Estimated Relative Risk<br>(95% C.I.) <sup>b</sup>                  | p-Value |
| Low                                                           | 154 | 0 (0.0)           | 1.03 (0.21,5.02)                                                    | 0.973   |
| Medium                                                        | 160 | 1 (0.6)           |                                                                     |         |
| High                                                          | 155 | 0 (0.0)           |                                                                     |         |

<sup>a</sup> Adjusted for percent body fat at the time of the blood measurement of dioxin.

<sup>b</sup> Relative risk for a twofold increase in initial dioxin.

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

| <b>(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED</b> |                                                   |         |
|-------------------------------------------------------------|---------------------------------------------------|---------|
| Analysis Results for Log <sub>2</sub> (Initial Dioxin)      |                                                   |         |
| n                                                           | Adjusted Relative Risk<br>(95% C.I.) <sup>a</sup> | p-Value |
| 466                                                         | 1.01 (0.20,5.08)                                  | 0.995   |

<sup>a</sup> Relative risk for a twofold increase in initial dioxin.

Note: Results are adjusted only for percent body fat at the time of the blood measurement of dioxin and lifetime alcohol history because of the sparse number of Ranch Hands with jaundice.

| <b>(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED</b> |       |                   |                                                |                    |
|---------------------------------------------------------------------------------|-------|-------------------|------------------------------------------------|--------------------|
| Dioxin Category                                                                 | n     | Number (%)<br>Yes | Est. Relative Risk<br>(95% C.I.) <sup>ab</sup> | p-Value            |
| Comparison                                                                      | 1,182 | 34 (2.9)          |                                                |                    |
| Background RH                                                                   | 370   | 11 (3.0)          | 1.05 (0.52,2.11)                               | 0.890              |
| Low RH                                                                          | 232   | 0 (0.0)           | --                                             | 0.017 <sup>c</sup> |
| High RH                                                                         | 237   | 1 (0.4)           | 0.14 (0.02,1.04)                               | 0.055              |
| Low plus High RH                                                                | 469   | 1 (0.2)           | --                                             | 0.001 <sup>c</sup> |

<sup>a</sup> Relative risk and confidence interval relative to Comparisons.

<sup>b</sup> Adjusted for percent body fat at the time of the blood measurement of dioxin.

<sup>c</sup> P-value determined using a chi-square test with continuity correction because of the sparse number of Ranch Hands with unspecified jaundice.

--: Results not presented because of the sparse number of Ranch Hands with unspecified jaundice.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

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

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

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

**Table 13-4. Analysis of Jaundice (Unspecified) (Continued)**

| <b>(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED</b> |       |                                                   |         |
|-------------------------------------------------------------------------------|-------|---------------------------------------------------|---------|
| Dioxin Category                                                               | n     | Adjusted Relative Risk<br>(95% C.I.) <sup>a</sup> | p-Value |
| Comparison                                                                    | 1,181 |                                                   |         |
| Background RH                                                                 | 367   | 0.99 (0.49,2.03)                                  | 0.988   |
| Low RH                                                                        | 231   | --                                                | --      |
| High RH                                                                       | 235   | 0.16 (0.02,1.20)                                  | 0.075   |
| Low plus High RH                                                              | 466   | --                                                | --      |

<sup>a</sup> Relative risk and confidence interval relative to Comparisons.

--: Results not presented because of the sparse number of Ranch Hands with unspecified jaundice.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin ≤ 10 ppt.

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

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

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

| <b>(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED</b> |     |                   |                                                            |
|------------------------------------------------------------|-----|-------------------|------------------------------------------------------------|
| 1987 Dioxin Category Summary Statistics                    |     |                   | Analysis Results for Log <sub>2</sub> (1987 Dioxin + 1)    |
| 1987 Dioxin                                                | n   | Number (%)<br>Yes | Estimated Relative Risk<br>(95% C.I.) <sup>a</sup> p-Value |
| Low                                                        | 281 | 8 (2.8)           | 0.44 (0.28,0.69) <0.001                                    |
| Medium                                                     | 276 | 3 (1.1)           |                                                            |
| High                                                       | 282 | 1 (0.4)           |                                                            |

<sup>a</sup> Relative risk for a twofold increase in 1987 dioxin.

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

| <b>(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED</b> |                                                   |  |         |
|----------------------------------------------------------|---------------------------------------------------|--|---------|
| Analysis Results for Log <sub>2</sub> (1987 Dioxin + 1)  |                                                   |  |         |
| n                                                        | Adjusted Relative Risk<br>(95% C.I.) <sup>a</sup> |  | p-Value |
| 833                                                      | 0.39 (0.24,0.65)                                  |  | <0.001  |

<sup>a</sup> Relative risk for a twofold increase in 1987 dioxin.

After covariate adjustment, the overall group difference remained significant (Table 13-4(b): Adj. RR=0.49, p=0.028). Stratifying by occupation revealed a marginally significant difference between Ranch Hands and Comparisons among the enlisted groundcrew (Table 13-4(b): Adj. RR=0.29, p=0.055).

Only one Ranch Hand had an extrapolated initial dioxin value. The Model 2 unadjusted analysis of jaundice was not significant (Table 13-4(c): p=0.973), nor was the adjusted analysis (Table 13-4(d): p=0.995).

The Model 3 unadjusted and adjusted analyses of jaundice each revealed a marginally significant difference between Ranch Hands in the high dioxin category and Comparisons (Table 13-4(e,f): Est. RR=0.14, p=0.055, for the unadjusted analysis; Adj. RR=0.16, p=0.075, for the adjusted analysis). The percentage of Ranch Hands in the high dioxin category with jaundice was 0.4 percent versus 2.9