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CHAPTER 13

GASTROINTESTINAL ASSESSMENT

INTRODUCTION

Background

This system assessment centers on reported peptic ulcer and liver disease, and current hepatic function and porphyria as determined by comprehensive laboratory testing and the physical examination. The liver is a major target organ for single high-dose and continued low-dose exposure to chlorophenols and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Peptic and stomach ulcer disease and porphyria cutanea tarda (PCT) are suspected clinical endpoints following moderate- to high-level exposures.

A variety of experimental animal studies[1-6] have demonstrated hepatic dysfunction and porphyria following a wide range of exposures to TCDD. The effects of exposure, as measured by enzymatic change, however, generally appear to be more related to species than to dose and route of administration.

Gross organ pathology in the digestive system and associated clinical symptoms have been observed following TCDD oral administration to animals (or by accidental ingestion). Pathological lesions have included gastric ulcers, metaplasia of the gastric mucosa, ileitus, hepatic hypertrophy and degeneration, hepatic parenchymal cell necrosis, and hepatic lipid accumulation.

Scientific interest has centered on changes in hepatic enzymes following TCDD administration. Studies involving the metabolism of TCDD have indicated that 74 to 81 percent of the intestinal uptake in rats is absorbed into the liver and adipose tissue, making the liver a key organ for TCDD effects.[7] Clearly, TCDD has proved to be an exceptional inducer of hepatic enzymes and mixed function oxidases, and a powerful inhibitor of other enzymes. Specifically, the induction of cytochrome P-450, a ferrocytochrome enzyme, has been demonstrated in many species and most of their tissues. Further, marked increases in cytochrome P-450 have been implicated as a mechanism of hepatotoxicity, although other factors, such as genetic susceptibility, are also contributory.[8-10]

Extensive work has been done investigating the TCDD-binding capacity of hepatic Ah receptors and the enhancement of lipid peroxidase and glutathione peroxidase activity in the presence of TCDD in a variety of experimental animals.[11-23] Other hepatic effects include the inhibition of cholesterol synthesis and fatty acid synthesis, a decrease in estrogen receptors, a change in the proteins found in plasma membranes, and an increase in liver weight as a result of hepatocellular hypertrophy.[7,24-27] TCDD has also been shown to cause the disruption of subcellular distributions of iron, copper, zinc, and magnesium.[28] Peroxisome proliferation has been shown with 2,4-D and 2,4,5-T and appears to depend on the location of the chlorine atoms on the phenoxy molecule.[29]

TCDD has also been shown to produce hepatic porphyria in animals by a reduction in uroporphyrinogen decarboxylase, possibly due to the activation of the P-450 enzyme.[30,31] The porphyriogenic effect of TCDD has also been influenced by genetic susceptibility, iron levels, sex, and ambient temperature.[32,33] In correlation with some human studies, hexachlorobenzene was found to be more porphyriogenic than TCDD.[32] Work in humans has located cytochrome P-450 receptors that bind TCDD in the liver.[34,35]

Numerous morbidity studies, predominantly from the industrial sector, have noted significant abnormal liver function in exposed workers, with and without the presence of clinical hepatic disease. Abnormal liver function test results have been found for direct bilirubin, alkaline phosphatase, triglycerides, cholesterol, aspartate aminotransferase (AST; previously called serum glutamic-oxaloacetic transaminase or SGOT), gamma-glutamyl transpeptidase (GGT; previously GGTP), urine d-glucaric acid, etc.[36-49] The consistent finding of elevated cholesterol levels may have predictive significance with respect to future heart disease (see Chapter 15).

Contemporary studies have focused on two indirect measures of hepatic microsomal activity, GGT and urine d-glucaric acid. In the study of an English industrial incident, several Seveso investigations, and two studies of the Monsanto plant in Nitro, West Virginia, there was modest agreement in observing elevated GGT and urine d-glucaric acid levels in exposed individuals.[41,42,44,45] Common to all studies was the observation that individuals with chloracne manifested significantly more abnormal liver function tests than exposed individuals without chloracne or unexposed individuals, suggesting a link to TCDD exposure.

Several industrial studies have shown altered porphyrin excretion patterns (predominantly an increase in uroporphyrin) or clinical evidence of PCT, particularly in chronically exposed workers.[50-52] Individuals with low chronic exposure or high acute exposure (Seveso) have not shown these signs. Reviews of the suspected association have identified the following difficulties in interpreting these studies: (1) multiple etiologies of PCT or abnormal porphyrin excretion patterns (chemical exposure, genetic makeup, alcohol consumption), (2) potential misdiagnosis of PCT, and (3) confounding by other chemical exposures in the industrial cohorts. Some investigators believe that the PCT cases found in the early U.S. and European studies were more likely caused by exposure to chlorobenzenes than to TCDD.[53] Overall, the evidence at present is inconclusive to establish a causal association between PCT and TCDD exposure.

A recent industrial study based on questionnaire data has suggested an association of stomach and peptic ulcers with exposure to TCDD.[43] This finding at the Monsanto plant differs from similar research using a slightly different cohort at the same plant that produced a negative conclusion on peptic ulcer disease.[44] The gastric ulcer-TCDD association has not been reported in other cohort dioxin morbidity studies, but ulcer disease has generally not been a major research focus. The preliminary gastric ulcer-TCDD association is fortified somewhat by studies that have shown significant gastric mucosal damage in monkeys following oral administration of TCDD.[2]

Baseline Summary Results

The 1982 Air Force Health Study (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 PCT, as well as detailed information on PCT risk factors (e.g., alcohol consumption, chemical exposures). The physical examination measured hepatomegaly 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 medical record reviews) 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.

The physical examination detected a twofold increase in hepatomegaly in the Ranch Hands, but the numbers were small and not statistically significant. Many analyses of the laboratory test variables involved group-by-covariate interactions. Ranch Hands had slightly higher GGT and lactic dehydrogenase (LDH) results and lower cholesterol levels; no differences were found for bilirubin or alkaline phosphatase levels.

AST, alanine aminotransferase (ALT; previously called serum glutamic-pyruvic transaminase or SGPT), and LDH results in the Ranch Hands interacted with the alcohol, degreasing chemicals, and industrial chemicals covariates differently than they did in the Comparisons. All of these two-factor interactions were statistically significant ($p<0.05$). There were no significant group differences in uroporphyrin, coproporphyrin, or d-aminolevulinic acid levels, nor did any test set support a diagnosis of PCT. Exposure analyses were essentially negative.

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

1985 Followup Study Summary Results

The 1985 AFHS examination continued the emphasis on hepatic function and expanded the porphyrin test battery to six assays. In addition, new components were added to the questionnaire to assess past and current diagnosed peptic ulcer disease, along with a series of screening questions to assess possible undiagnosed disease. Covariate data on aspirin usage, blood group, and family history of peptic ulcer and additional probes on intestinal parasites, gallbladder disease, and other liver conditions were also added. Because of the known effects of alcohol ingestion on hepatic function, a detailed alcohol consumption history was obtained by questionnaire.

The interval questionnaire revealed sparse reporting of liver disorders from 1982 to 1985 that was not significantly different between groups. 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 medical record verifica-

tion process showed that the historical data were generally correctly reported and classified between groups, except for the category of enlarged liver, which showed a higher verification rate in the Comparison group.

No differences were found for past or current peptic ulcer disease in the Ranch Hand and Comparison groups, after adjustment for blood type.

The physical examination disclosed a borderline significant increase of hepatomegaly in the Ranch Hand group. Emphasis was placed on nine laboratory test variables measuring liver function, i.e., AST, ALT, GGT, alkaline phosphatase, total and direct bilirubin, LDH, cholesterol, and triglycerides. In addition, uroporphyrin and coproporphyrin measurements were obtained to assess liver function and the likelihood of PCT. The nine hepatic variables were subjected to continuous and discrete statistical tests, and were adjusted for the covariates of age, race, occupation, current alcohol use, and unprotected exposure to both industrial chemicals and degreasing chemicals. Final statistical models used only the significant covariates and two-way interactions for adjustment. The two porphyrin measurements were analyzed only in the continuous form.

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 the Ranch Hands. Only in the instance of alkaline phosphatase was the discrete analysis statistically significant. No group differences were noted for AST, GGT, total and direct bilirubin, LDH, cholesterol, or triglycerides. A review of the covariate effects in the adjusted statistical models revealed that all covariates behaved as expected with the exception of alcohol consumption for the alkaline phosphatase analysis, which showed an inverse relationship with wine consumption.

Exploration of group-by-covariate interactions for alkaline phosphatase, direct bilirubin, triglycerides, AST, and uroporphyrins revealed significant group differences within specific covariate strata. In particular, Ranch Hands exposed to industrial chemicals had a significantly higher adjusted mean level of alkaline phosphatase and a significantly higher prevalence rate of abnormal direct bilirubin levels than similarly exposed Comparisons. For triglycerides, Ranch Hands born in or before 1922 had a significantly higher adjusted mean level than similar aged Comparisons, while Ranch Hand officers exhibited a significantly higher prevalence rate of abnormal levels than Comparison officers. For AST, Ranch Hand moderate current drinkers (more than one to four drinks per day) had a significantly higher mean level than corresponding Comparisons. In the opposite direction, Comparisons with a mean blood urea nitrogen level less than or equal to 14 mg/dl (median for all participants) were found to have a significantly higher adjusted mean uroporphyrin level than similar Ranch Hands. These results did not disclose any common pattern suggesting a detriment in the Ranch Hand group.

These findings were generally consistent with the 1982 Baseline data. Slight differences in analytic results are probably due to the use of more fully adjusted models used for the 1985 followup examination data.

Overall, the followup examination laboratory data showed no adverse clinical or exposure patterns in either group. Further, the detection of

significant mean shifts (still within normal range) by the continuous statistical tests, not mirrored by the discrete tests, highlights the difference between statistical significance and biological relevance.

The results of the exposure index analyses were generally not significant. Significant or marginally significant results that supported a herbicide effect were found for ALT and total bilirubin in the enlisted flyer cohort, and for AST in the enlisted groundcrew cohort.

Longitudinal analyses for AST, ALT, and GGT disclosed no statistically significant group differences in the mean shifts from the Baseline to the 1985 followup examination.

Interval reporting of PCT-like symptoms of skin patches, bruises, and sensitivity was significantly increased in the Ranch Hands. However, when these historic data were contrasted to both uroporphyrin and coproporphyrin abnormalities, no correlation was apparent, nor were there any significant group differences. Since an elevation in the uroporphyrin level is required for a diagnosis of PCT, the historic data were retabulated with only uroporphyrin abnormalities; again, no group differences were apparent, and uroporphyrin abnormalities in both groups were higher in those participants without a history of skin disorders than in those participants with such a history. The likelihood of bona fide PCT among study participants, and particularly among the Ranch Hands, appears to be remote.

The 1985 followup examination disclosed more statistically significant findings for tests of liver function than the Baseline examination, but they were equally divided between the two groups and did not demonstrate clinical, statistical, or exposure patterns consistent with a herbicide-related effect on health. No evidence was found to suggest an increased likelihood of PCT in the Ranch Hand group.

Parameters of the 1987 Gastrointestinal Assessment

Dependent Variables

Questionnaire, physical examination, and laboratory data were used in the 1987 gastrointestinal assessment.

Questionnaire Data

During the 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 verified by medical record review. The verified results were then grouped into eight categories of disorders for analysis: viral hepatitis, acute and subacute necrosis of the liver, chronic liver disease and cirrhosis (alcoholic-related and non-alcoholic-related were analyzed separately), liver abscess and sequelae of chronic liver disease, other disorders of the liver, jaundice (unspecified, not of the newborn), and hepatomegaly.

Information on the occurrence of peptic or stomach ulcers and on skin bruises, patches, and sensitivity was also captured in the questionnaire. This self-reported information was analyzed as part of the 1987 assessment. A verified ulcer variable based on gastric, duodenal, peptic, and gastrojejunal ulcers was also analyzed.

For each condition (other than reported ulcer and skin patches, bruises, and sensitivity), participants with a pre-Southeast Asia (SEA) diagnosis were excluded from the analysis.

The frequency of digestive system mortality was tabulated.

Physical Examination Data

One variable from the physical examination, diagnosed hepatomegaly, was analyzed in the gastrointestinal assessment. This variable was coded as yes/no.

Participants whose blood contained hepatitis B surface antigen (HB_sAg) were excluded from the analysis of hepatomegaly.

Laboratory Examination Data

The 1987 followup examination emphasized evaluation of laboratory data, particularly for the hepatic function. Thirteen laboratory variables were analyzed: 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), high-density lipoproteins (HDL in mg/dl), cholesterol-HDL radio, triglycerides (mg/dl), creatine kinase (U/L), and fasting glucose (mg/dl). Each of these was analyzed as a continuous variable and as a discrete variable. All were dichotomized as normal versus high for the discrete analyses except HDL, which was dichotomized as normal versus low. For all variables other than HDL, only values greater than the normal range were considered as important in the assessment of dysfunction and coded as abnormal. A natural logarithm transformation was applied to all the variables except HDL and cholesterol-HDL ratio. These two exceptions were analyzed in original units. For total bilirubin and direct bilirubin, the transformation was done after adding 0.1 to each value because several participants had levels of 0 mg/dl.

Participants whose blood contained HB_sAg and participants with body temperature greater than or equal to 100 degrees Fahrenheit were excluded from the analysis of the laboratory variables.

Covariates

The effects of covariates were examined in the gastrointestinal assessment, both in pairwise associations with the dependent variables and in adjusted statistical analyses. Blood type was a candidate covariate for the adjusted analysis of reported and verified ulcer. The matching variables age, race, and occupation were used for analyses with all laboratory variables. In addition, current alcohol use, lifetime alcohol history, lifetime industrial

chemical exposure, and lifetime degreasing chemical exposure were candidate covariates for the adjusted analyses of all of the laboratory variables except alkaline phosphatase. For alkaline phosphatase, current wine consumption was used instead of current alcohol use, and lifetime wine history was used instead of lifetime alcohol history since wine consumption showed a strong negative association with alkaline phosphatase in the 1985 followup.

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

Age, current alcohol use, and lifetime alcohol history were treated as continuous variables for all adjusted analyses. However, for the discrete covariate tests of association, and to explore interactions, they were categorized for presentation. Current wine use and lifetime wine history were treated as continuous variables for the adjusted alkaline phosphatase analyses, and were similarly categorized for presentation. Degreasing chemical exposure and industrial chemical exposure were categorized for all analyses. The cutpoints used for categorization are specified in Table 13-1. In discussing the alcohol-related covariates, the terms light, moderate, and heavy are frequently used to describe the current drinking habits of the participants; for lifetime alcohol use, never replaces light. These distinctions correspond to the three drinking categories in Table 13-1 for current alcohol use and lifetime drinking history.

Relation to Baseline and 1985 Followup Studies

The verified questionnaire data analyzed in the 1987 assessment were organized by International Classification of Disease (ICD) medical coding categories. The analysis of ulcers was added in the 1985 assessment.

For the laboratory variables, the 1987 assessment was expanded to include HDL, cholesterol-HDL ratio, creatine kinase, and fasting glucose; all other laboratory variables analyzed in the 1987 followup were analyzed in the Baseline and 1985 followup studies.

The longitudinal assessment was based on the analysis of AST, ALT, and GGT.

Statistical Methods

The basic statistical analysis methods used in the gastrointestinal assessment are described in Chapter 7.

Table 13-1 summarizes the statistical analyses performed for the 1987 gastrointestinal assessment. The first part of this table identifies the dependent variables, source of the data, form(s) of the data, cutpoints,

TABLE 13-1.

Statistical Analysis for the Gastrointestinal Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Viral Hepatitis	Q-V	D	Yes No	--	UC:FT
Acute and Sub-acute Necrosis of the Liver	Q-V	D	Yes No	--	UC:FT
Chronic Liver Disease and Cirrhosis (Alcohol Related)	Q-V	D	Yes No	--	UC:FT
Chronic Liver Disease and Cirrhosis (Non-alcohol Related)	Q-V	D	Yes No	--	UC:FT
Liver Abscess and Sequelae of Chronic Liver Disease	Q-V	D	Yes No	--	UC:FT
Other Disorders of the Liver	Q-V	D	Yes No	--	UC:FT
Jaundice (Unspecified)	Q-V	D	Yes No	--	UC:FT
Hepatomegaly	Q-V	D	Yes No	--	UC:FT
Reported Ulcer	Q-SR	D	Yes-Current Yes-Past No	BLOOD	UC:CS AC:LL
Skin Bruises, Patches, or Sensitivity	Q-SR	D	Yes No	--	UC:FT
Verified Ulcer	Q-V	D	Yes No	BLOOD	UC:FT AC:LR

TABLE 13-1. (continued)

Statistical Analysis for the Gastrointestinal Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Diagnosed Hepatomegaly	PE	D	Yes No	AGE RACE OCC ALC DRKYR IC DC	UC:FT AC:LR CA:CS,FT
AST (U/L)	LAB	D/C	Normal: <47 High: ≥48	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM L:RM
ALT (U/L)	LAB	D/C	Normal: <36 High: ≥37	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM L:RM
GGT (U/L)	LAB	D/C	Normal: <85 High: ≥86	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM L:RM
Alkaline Phosphatase (U/L)	LAB	D/C	Normal: <136 High: ≥137	AGE RACE OCC WINE LWINE IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM

TABLE 13-1. (continued)

Statistical Analysis for the Gastrointestinal Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Total Bilirubin (mg/dl)	LAB	D/C	Normal: <1.5 High: ≥1.5	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM
Direct Bilirubin (mg/dl)	LAB	D/C	Normal: ≤0.40 High: ≥0.41	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM
LDH (U/L)	LAB	D/C	Normal: ≤190 High: ≥191	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM
Cholesterol (mg/dl)	LAB	D/C	Normal: ≤260 High: ≥261	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM
HDL (mg/dl)	LAB	D/C	Normal: ≥25 Low: <25	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM

TABLE 13-1. (continued)

Statistical Analysis for the Gastrointestinal Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Cholesterol-HDL Ratio	LAB	D/C	Normal: ≤5 High: >5	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT
Triglycerides (mg/dl)	LAB	D/C	Normal: ≤320 High: ≥321	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM
Creatine Kinase (U/L)	LAB	D/C	Normal: ≤232 High: ≥233	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM
Fasting Glucose (mg/dl)	LAB	D/C	Normal: ≤110 High: ≥111	AGE RACE OCC ALC DRKYR IC DC	UC:FT,TT AC:LR,GLM CA:CC,TT,GLM,CS,FT UE:CS,FT,GLM,TT AE:LR,GLM

TABLE 13-1. (continued)

Statistical Analysis for the Gastrointestinal Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born >1942 Born 1923-1941 Born ≤1922
Race (RACE)	MIL	D	Nonblack Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Current Alcohol Use (ALC) (drinks/day)	Q-SR	D/C	0-1 >1-4 >4
Current Wine Use (WINE) (drinks/day)	Q-SR	D/C	0 >0
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	D/C	0 >0-40 >40
Lifetime Wine History (LWINE) (drink-years of wine)	Q-SR	D/C	0 >0-10 >10
Industrial Chemical Exposure (IC)	Q-SR	D	Yes No
Degreasing Chemical Exposure (DC)	Q-SR	D	Yes No
Blood Type (BLOOD)	MIL	D	A B AB O

Abbreviations:

Data Source:
LAB--1987 SCRF laboratory results
MIL--Air Force military records
PE--1987 SCRF physical examination
Q-SR--1987 NORC questionnaire (self-reported)
Q-V--1987 NORC questionnaire (verified)

TABLE 13-1. (continued)

Statistical Analysis for the Gastrointestinal Assessment

Abbreviations (continued):

Data Form:	D--Discrete analysis only D/C--Discrete and continuous analyses for dependent variables; appropriate form for analysis (either discrete or continuous) for covariates
Statistical Analyses:	UC--Unadjusted core analyses AC--Adjusted core analyses CA--Dependent variable-covariate associations UE--Unadjusted exposure index analyses AE--Adjusted exposure index analyses L--Longitudinal analyses
Statistical Methods:	CC--Pearson's product moment correlation coefficient CS--Chi-square contingency table test FT--Fisher's exact test GLM--General linear models analysis LL--Log-linear models analysis LR--Logistic regression analysis RM--Repeated measures analysis TT--Two-sample t-test

candidate covariates, and statistical methods. The second part of the table provides additional information on the candidate covariates. Abbreviations are used extensively in the body of the table and are defined in footnotes.

Dependent variable and covariate data were missing for some participants. Table 13-2 summarizes the number of participants with missing data, and the number who were excluded from analyses for medical reasons, by group and variable.

RESULTS

Ranch Hand and Comparison Group Contrast

Table 13-3 presents unadjusted results for verified questionnaire variables. Unadjusted results for ulcers, presence of skin bruises, patches, or sensitivity, and diagnosed hepatomegaly are given in Table 13-4; adjusted results for hepatomegaly and peptic ulcer are shown in Table 13-5. Unadjusted and adjusted results for the laboratory examination variables are provided in Tables 13-6 and 13-7, respectively. Table J-1 of Appendix J summarizes the results of the covariate tests of association for hepatomegaly and the laboratory examination variables. Table J-2 details the relationship between ulcer and blood type. Stratified results to explore group-by-covariate interactions are presented in Table J-3.

Questionnaire Variables

Verified questionnaire data on viral hepatitis, acute and subacute necrosis of the liver, chronic liver disease and cirrhosis (alcohol-related and nonalcohol-related analyzed separately), liver abscess and sequelae of chronic liver disease, other disorders of the liver, jaundice (unspecified, not of newborn), and hepatomegaly were analyzed. Additional self-reported information from the questionnaire was analyzed on occurrences of ulcers, and on skin patches, bruises, and sensitivity. As seen in Tables 13-3 and 13-4, no significant group differences were noted for any of these conditions.

An additional analysis was done for reported ulcer, adjusting for blood type and the group-by-blood type interaction. However, since neither of these effects were statistically significant, they were deleted from the adjusted model. Thus, results for this adjusted analysis paralleled the unadjusted analysis.

Verified Ulcer

The unadjusted prevalence of verified ulcer was not significantly different between groups ($p=0.950$). An adjusted analysis was done examining the effects of blood type and the group-by-blood type interaction. This analysis found no significant result.

TABLE 13-2.

Number of Participants Excluded and With Missing Data for the Gastrointestinal Assessment by Group

Variable	Analysis Use	Group		Total
		Ranch Hand	Comparison	
All 13 Laboratory Examination Variables	DEP	1	2	3
Reported Ulcer	DEP	1	0	1
Current Alcohol Use	COV	5	1	6
Current Wine Use	COV	6	2	8
Lifetime Alcohol History	COV	10	3	13
Lifetime Wine History	COV	6	3	9
Blood Type	COV	6	7	13
Pre-SEA Viral Hepatitis	EXC	27	42	69
Pre-SEA Acute and Subacute Necrosis of the Liver	EXC	0	1	1
Pre-SEA Chronic Liver Disease and Cirrhosis (Alcohol-Related)	EXC	1	5	6

TABLE 13-2. (continued)

Number of Participants Excluded and With Missing Data for the Gastrointestinal Assessment by Group

Variable	Analysis Use	Group		Total
		Ranch Hand	Comparison	
Pre-SEA Chronic Liver Disease and Cirrhosis (Nonalcohol-Related)	EXC	0	1	1
Pre-SEA Other Disorders of the Liver	EXC	6	12	18
Pre-SEA Jaundice	EXC	27	39	66
Pre-SEA Hepatomegaly	EXC	2	2	4
Pre-SEA Verified Ulcer	EXC	23	32	55
Positive HB_sAg	EXC	7	8	15
Temperature $\geq 100°$ at Laboratory Examination	EXC	1	3	4

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

TABLE 13-3.

Unadjusted Analysis for Verified Gastrointestinal Questionnaire Variables by Group

Variable	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Viral Hepatitis	n	968		1,257			
	Number/%						
	Yes	375	38.7%	510	40.6%	0.93 (0.78,1.10)	0.406
	No	593	61.3%	747	59.4%		
Acute and Sub-acute Necrosis of the Liver	n	995		1,298			
	Number/%						
	Yes	0	0.0%	2	0.2%	--[a]	0.640
	No	995	100.0%	1,296	99.8%		
Chronic Liver Disease and Cirrhosis (Alcohol Related)	n	994		1,294			
	Number/%						
	Yes	46	4.6%	51	3.9%	1.18 (0.79,1.78)	0.480
	No	948	95.4%	1,243	96.1%		
Chronic Liver Disease and Cirrhosis (Non-alcohol Related)	n	995		1,298			
	Number/%						
	Yes	11	1.1%	9	0.7%	1.60 (0.66,3.88)	0.408
	No	984	98.9%	1,289	99.3%		
Liver Abscess and Sequelae of Chronic Liver Disease	n	995		1,299			
	Number/%						
	Yes	0	0.0%	1	0.1%	--[a]	0.999
	No	995	100.0%	1,298	99.9%		

TABLE 13-3. (continued)

Unadjusted Analysis for Verified Gastrointestinal Questionnaire Variables by Group

Variable	Statistic	Group				Est. Relative Risk (95% C.I.)	p-Value
		Ranch Hand		Comparison			
Other Disorders of the Liver	n	989		1,287			
	Number/%						
	Yes	90	9.1%	95	7.4%	1.26 (0.93,1.70)	0.159
	No	899	90.9%	1,192	92.6%		
Jaundice (Unspecified)	n	968		1,260			
	Number/%						
	Yes	17	1.8%	32	2.5%	0.69 (0.38,1.24)	0.268
	No	951	98.2%	1,228	97.5%		
Hepatomegaly	n	993		1,297			
	Number/%						
	Yes	16	1.6%	25	1.9%	0.83 (0.44,1.57)	0.690
	No	977	98.4%	1,272	98.1%		

[a]Estimated relative risk/confidence interval not given due to a cell with zero frequency.

TABLE 13-4.

Unadjusted Analysis for Other Gastrointestinal Questionnaire and Physical Examination Variables by Group

Variable	Statistic	Group: Ranch Hand		Group: Comparison		Contrast	Est. Relative Risk (95% C.I.)	p-Value
Reported Ulcer	n	994		1,299				
	Number/%							
	Yes-Current	11	1.1%	10	0.8%	Overall		0.688
	Yes-Past	10	1.0%	12	0.9%	Yes-Current vs. No	1.44 (0.61,3.41)	0.532
	No	973	97.9%	1,277	98.3%	Yes-Past vs. No	1.09 (0.47,2.54)	0.998
Verified Ulcer (Questionnaire and Physical Exam)	n	972		1,267				
	Number/%							
	Yes	69	7.1%	92	7.3%		0.98 (0.71,1.35)	0.950
	No	903	92.9%	1,175	92.7%			
Skin Bruises, Patches, or Sensitivity	n	995		1,299				
	Number/%							
	Yes	184	18.5%	207	15.9%		1.20 (0.96,1.49)	0.120
	No	811	81.5%	1,092	84.1%			
Diagnosed Hepatomegaly (Physical Exam)	n	988		1,291				
	Number/%							
	Yes	11	1.1%	15	1.2%		0.96 (0.44,2.10)	0.999
	No	977	98.9%	1,276	98.8%			

TABLE 13-5.

Adjusted Analysis for Reported Gastrointestinal Questionnaire and Physical Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Reported Ulcer	n	994	1,299	Overall Yes-Current vs. No Yes-Past vs. No	 1.44 (0.61,3.41) 1.09 (0.47,2.54)	0.688 0.532 0.998	—
Verified Ulcer (Questionnaire and Physical Exam)	n	972	1,267		0.98 (0.71,1.35)	0.950	—
Diagnosed Hepatomegaly (Physical Exam)	n	978	1,288		0.95 (0.43,2.07)**	0.888**	GRP*DC (p=0.016) OCC (p=0.049) RACE*DRKYR (p=0.031)

—No covariates significant in final model (p>0.05).

GRP: Group (Ranch Hand, Comparison).

**Group-by-covariate interaction (0.01≤p<0.05)—adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

TABLE 13-6.

Unadjusted Analysis for Hepatic Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
AST	n	986	1,286		
	Mean[a]	25.8	25.6	--	0.695
	95% C.I.[a]	(25.3,26.3)	(25.2,26.1)		
	Number/%				
	High	48 4.9%	54 4.2%	1.17 (0.78,1.74)	0.508
	Normal	938 95.1%	1,232 95.8%		
ALT	n	986	1,286		
	Mean[a]	20.6	20.7	--	0.817
	95% C.I.[a]	(19.9,21.2)	(20.1,21.2)		
	Number/%				
	High	120 12.2%	144 11.2%	1.10 (0.85,1.42)	0.514
	Normal	866 87.8%	1,142 88.8%		
GGT	n	986	1,286		
	Mean[a]	33.2	32.6	--	0.552
	95% C.I.[a]	(31.8,34.6)	(31.5,33.8)		
	Number/%				
	High	83 8.4%	104 8.1%	1.05 (0.77,1.41)	0.834
	Normal	903 91.6%	1,182 91.9%		
Alkaline Phosphatase	n	986	1,286		
	Mean[a]	93.7	90.3	--	<0.001
	95% C.I.[a]	(92.3,95.1)	(89.1,91.5)		
	Number/%				
	High	48 4.9%	62 4.8%	1.01 (0.69,1.49)	0.999
	Normal	938 95.1%	1,224 95.2%		

TABLE 13-6. (continued)

Unadjusted Analysis for Hepatic Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
Total Bilirubin	n	986	1,286		
	Mean[b]	0.780	0.785	--	0.611
	95% C.I.[b]	(0.765,0.795)	(0.771,0.800)		
	Number/%				
	High	28 2.8%	48 3.7%	0.75 (0.47,1.21)	0.292
	Normal	958 97.2%	1,238 96.3%		
Direct Bilirubin	n	986	1,286		
	Mean[b]	0.158	0.158	--	0.969
	95% C.I.[b]	(0.151,0.165)	(0.151,0.165)		
	Number/%				
	High	35 3.5%	57 4.4%	0.79 (0.52,1.22)	0.342
	Normal	951 96.5%	1,229 95.6%		
LDH	n	986	1,286		
	Mean[a]	128.1	127.8	--	0.692
	95% C.I.[a]	(126.8,129.5)	(126.6,129.0)		
	Number/%				
	High	12 1.2%	16 1.2%	0.98 (0.46,2.08)	0.999
	Normal	974 98.8%	1,270 98.8%		
Cholesterol	n	986	1,286		
	Mean[a]	214.8	213.4	--	0.379
	95% C.I.[a]	(212.3,217.3)	(211.3,215.5)		
	Number/%				
	High	141 14.3%	158 12.3%	1.19 (0.93,1.52)	0.179
	Normal	845 85.7%	1,128 87.7%		

TABLE 13-6. (continued)

Unadjusted Analysis for Hepatic Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
HDL	n	986	1,286		
	Mean	49.08	49.18	--	0.847
	95% C.I.	(47.83,50.38)	(47.99,50.37)		
	Number/%				
	Low	9 0.9%	13 1.0%	0.90 (0.38,2.12)	0.992
	Normal	977 99.1%	1,273 99.0%		
Cholesterol-HDL Ratio	n	986	1,286		
	Mean	4.75	4.70	--	0.357
	95% C.I.	(4.60,4.90)	(4.56,4.84)		
	Number/%				
	High	432 43.8%	537 41.8%	1.09 (0.92,1.29)	0.348
	Normal	554 56.2%	749 58.2%		
Triglycerides	n	986	1,286		
	Mean[a]	119.5	116.5	--	0.355
	95% C.I.[a]	(114.8,124.4)	(112.6,120.6)		
	Number/%				
	High	66 6.7%	70 5.4%	1.25 (0.88,1.76)	0.248
	Normal	920 93.3%	1,216 94.6%		
Creatine Kinase	n	986	1,286		
	Mean[a]	110.0	108.8	--	0.611
	95% C.I.[a]	(106.8,113.4)	(105.7,112.1)		
	Number/%				
	High	57 5.8%	97 7.5%	0.75 (0.54,1.06)	0.114
	Normal	929 94.2%	1,189 92.5%		

TABLE 13-6. (continued)

Unadjusted Analysis for Hepatic Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Est. Relative Risk (95% C.I.)	p-Value
Fasting Glucose	n	986	1,286		
	Mean[a]	100.6	100.1	--	0.504
	95% C.I.[a]	(99.5,101.7)	(99.3,100.9)		
	Number/%				
	High	120 12.2%	167 13.0%	0.93 (0.72,1.19)	0.606
	Normal	866 87.8%	1,119 87.0%		

--Estimated relative risk not applicable for continuous analysis of a variable.

[a]Transformed from natural logarithm scale.

[b]Transformed from natural logarithm (X + 0.1) scale.

TABLE 13-7.

Adjusted Analysis for Hepatic Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
AST	n	981	1,285			ALC*RACE (p=0.016)
	Adj. Mean[a]	26.7	26.5	--	0.453	ALC*IC (p=0.028)
	95% C.I.[a]	(25.9,27.6)	(25.7,27.3)			
	n	981	1,285	1.23 (0.82,1.84)	0.326	ALC (p<0.001)
ALT	n	976	1,283			GRP*DRKYR (p=0.020)
	Adj. Mean**[a]	20.8	20.7	--	0.915**	AGE (p<0.001)
	95% C.I.**[a]	(19.7,21.8)	(19.8,21.7)			ALC*RACE (p<0.001)
						ALC*IC (p=0.011)
						DC*IC (p=0.038)
	n	981	1,285	1.14 (0.88,1.49)	0.313	AGE*OCC (p=0.003)
						AGE*IC (p=0.009)
						ALC*IC (p=0.031)
GGT	n	976	1,283			RACE (p<0.001)
	Adj. Mean[a]	37.6	36.7	--	0.365	DC (p=0.022)
	95% C.I.[a]	(35.2,40.1)	(34.5,39.0)			ALC*DRKYR (p<0.001)
	n	976	1,283	1.07 (0.78,1.46)	0.695	OCC*DC (p=0.043)
						RACE*DC (p=0.038)
						ALC*DRKYR (p=0.028)

TABLE 13-7. (continued)

Adjusted Analysis for Hepatic Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Alkaline Phosphatase	n	979	1,283			AGE (p<0.001)
	Adj. Mean[a]	93.4	89.9	--	<0.001	LWINE (p=0.028)
	95% C.I.[a]	(91.1,95.7)	(87.8,92.1)			OCC*WINE (p=0.007)
						RACE*IC (p=0.006)
	n	979	1,283	1.03 (0.70,1.52)	0.892	AGE (p<0.001)
						IC (p=0.003)
						LWINE (p=0.013)
Total Bilirubin	n	976	1,283			ALC*DRKYR (p=0.023)
	Adj. Mean[b]	0.778	0.784	--	0.622	AGE*IC (p=0.032)
	95% C.I.[b]	(0.763,0.794)	(0.770,0.798)			
	n	976	1,283	0.75 (0.47,1.21)**	0.237**	GRP*ALC (p=0.036)
						GRP*DRKYR (p=0.040)
Direct Bilirubin	n	986	1,286			GRP*RACE (p=0.022)
	Adj. Mean**[b]	0.156	0.156	--	0.985**	OCC (p=0.029)
	95% C.I.**[b]	(0.148,0.164)	(0.149,0.163)			
	n	986	1,286	****	****	GRP*DC (p=0.009)
						OCC (p=0.044)
LDH	n	976	1,283			ALC*DRKYR (p=0.025)
	Adj. Mean[a]	127.3	127.1	--	0.804	AGE*OCC (p=0.025)
	95% C.I.[a]	(125.9,128.8)	(125.8,128.4)			
	n	986	1,286	0.98 (0.46,2.08)	0.954	--

TABLE 13-7. (continued)

Adjusted Analysis for Hepatic Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Cholesterol	n Adj. Mean[a] 95% C.I.[a]	981 216.2 (211.4,221.2)	1,285 215.0 (210.3,219.7)	--	0.437	AGE (p<0.001) ALC (p=0.021) IC (p=0.023) OCC*RACE (p=0.003)
	n	986	1,286	1.18 (0.93,1.51)	0.177	AGE (p=0.048) OCC (p=0.034)
HDL	n Adj. Mean** 95% C.I.**	976 48.31 (46.03,50.63)	1,283 47.71 (45.72,49.70)	--	0.648**	GRP*DRKYR (p=0.036) OCC (p=0.042) ALC (p=0.001) RACE*DC (p=0.004) ALC*DRKYR (p<0.001) RACE*IC (p=0.042)
	n	976	1,283	1.01 (0.42,2.45)	0.999	DC (p=0.040)
Cholesterol-HDL Ratio	n Adj. Mean 95% C.I.	976 4.77 (4.48,5.05)	1,283 4.89 (4.64,5.13)	--	0.509	ALC (p=0.002) RACE*DC (p=0.017) AGE*DRKYR (p=0.040) ALC*DRKYR (p=0.004)
	n	976	1,283	1.07 (0.90,1.27)	0.434	AGE (p=0.038) RACE (p=0.036) OCC (p<0.001) ALC (p<0.001)

TABLE 13-7. (continued)

Adjusted Analysis for Hepatic Laboratory Examination Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Triglycerides	n	976	1,283			AGE (p<0.001)
	Adj. Mean[a]	107.8	105.6	--	0.459	OCC (p=0.001)
	95% C.I.[a]	(101.0,115.0)	(99.4,112.3)			DC (p=0.009)
						DRKYR*RACE (p=0.038)
	n	976	1,283	1.28 (0.90,1.82)	0.172	RACE (p=0.039)
						ALC*DRKYR (p=0.043)
Creatine Kinase	n	981	1,285			AGE (p=0.002)
	Adj. Mean[a]	145.4	143.4	--	0.500	RACE (p<0.001)
	95% C.I.[a]	(138.2,153.0)	(136.7,150.5)			ALC*OCC (p=0.045)
	n	986	1,286	0.76 (0.53,1.08)	0.122	RACE (p<0.001)
						AGE*DC (p=0.019)

TABLE 13-7. (continued)

Adjusted Analysis for Hepatic Laboratory Examination Variables by Group

Variable	Statistic	Group		Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
		Ranch Hand	Comparison			
Fasting Glucose	n	976	1,283			DRKYR*OCC (p<0.001)
	Adj. Mean[a]	102.5	102.0	--	0.534	AGE*RACE (p=0.002)
	95% C.I.[a]	(100.8,104.2)	(100.4,103.7)			DRKYR*RACE (p=0.050)
	n	976	1,283	0.93 (0.72,1.20)	0.565	AGE (p<0.001)
						RACE (p=0.008)
						DC (p=0.024)
						DRKYR (p=0.021)

[a]Transformed from natural logarithm scale.

--Adjusted relative risk not applicable for continuous analysis of a variable; no covariates significant in final model (p>0.05).

[b]Transformed from natural logarithm (X + 0.1) scale.

**Group-by-covariate interaction (0.01<p≤0.05)--adjusted means or relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

****Group-by-covariate interaction (p≤0.01)--adjusted relative risk, confidence interval, and p-value not presented.

Physical Examination Variables

Diagnosed Hepatomegaly

The percentage of participants diagnosed with hepatomegaly at the physical examination did not differ significantly between groups ($p=0.999$).

Using pooled group data, the covariate tests of association showed that hepatomegaly was associated with current alcohol use ($p=0.019$) and lifetime alcohol history ($p=0.016$). The percentages of participants with hepatomegaly increased with current alcohol use (0.9%, 1.8%, and 4.1% for the $\leq$1 drink/day, >1-4 drinks/day, and >4 drinks/day categories, respectively). Relatively fewer cases of hepatomegaly were seen for moderate lifetime drinkers (0.7% for individuals who drank and had at most 40 drink-years) than for men who had never drunk (2.0%) or for heavy lifetime drinkers (2.1% for men who had more than 40 drink-years).

A significant group-by-degreasing chemical exposure interaction was detected for the adjusted analysis ($p=0.016$). Occupation ($p=0.049$) and a race-by-lifetime alcohol history interaction ($p=0.031$) were also included for adjustment. Results were derived for each level of degreasing chemical exposure to explore the interaction. They showed that the adjusted group relative risk for participants who had never been exposed to degreasing chemicals was marginally less than one (Adj. RR: 0.27, 95% C.I.: [0.06,1.26], $p=0.095$). Conversely, the relative risk for individuals who had been exposed to degreasing chemicals was greater than one, but not significant (Adj. RR: 2.04, 95% C.I.: [0.72,5.81], $p=0.181$). Further analysis was done excluding the group-by degreasing chemical interaction. No significant group difference was found ($p=0.888$) after adjusting for the race-by-lifetime alcohol history interaction ($p=0.037$).

Laboratory Examination Variables

AST

Group differences for AST were not significant for both the unadjusted continuous ($p=0.695$) and discrete ($p=0.508$) analyses.

Examining the relationship between AST and the covariates revealed significant associations with race ($p=0.004$), current alcohol use ($p<0.001$), and lifetime alcohol history ($p<0.001$). A marginally significant association with degreasing chemical exposure was also found ($p=0.091$). Blacks had a higher mean level than nonblacks (27.7 U/L vs. 25.6 U/L). Both alcohol-related variables were positively correlated with AST ($r=0.220$ for current alcohol use; $r=0.096$ for lifetime alcohol history). Correspondingly, the percentage of abnormal AST values increased with current alcohol use (2.8%, 9.6%, and 19.2% for $\leq$1 drink/day, >1-4 drinks/day, and >4 drinks/day, respectively), but this pattern was not observed for lifetime alcohol history. The highest percentage of abnormal values was found for the heaviest drinkers (8.4% for participants with >40 drink-years), but men who had never drunk showed a slightly higher percentage of abnormalities than moderate drinkers

(3.9% vs. 3.2% for men with 0 drink-years and >0-40 drink-years, respectively). Relatively more AST abnormal levels were found for participants exposed to degreasing chemicals (5.1%) than for those who had not been exposed (3.5%).

Group differences remained nonsignificant after covariate adjustment ($p=0.453$, $p=0.326$ for the continuous and discrete analysis, respectively). The continuous model was adjusted for interactions between current alcohol use and race ($p=0.016$), and between current alcohol use and industrial chemical exposure ($p=0.028$). The discrete analysis was adjusted only for current alcohol use ($p<0.001$).

ALT

No significant group difference for ALT was found for either the unadjusted continuous ($p=0.817$) or discrete ($p=0.514$) analysis.

The relationship between ALT and the covariates was examined using pooled group data. As seen in Table J-1, significant associations were found with age, both alcohol-related variables, and degreasing chemical exposure. Age was negatively correlated with ALT ($r=-0.109$, $p<0.001$). This finding was also seen after categorizing ALT; the percentage of abnormalities decreased with age (14.3% abnormal values for participants born in or after 1942, 10.0% abnormal values for participants born between 1923 and 1941, and 4.8% abnormal values for participants born in or before 1922, $p=0.001$). The correlation with current alcohol use was 0.125 ($p<0.001$). Correspondingly, the percentage of abnormal levels increased with current alcohol use (10.2%, 17.0%, and 19.2% for individuals currently drinking ≤ 1 drink/day, >1-4 drinks/day, and >4 drinks/day, respectively; $p<0.001$). The percentages of abnormal values were 14.2 percent, 10.1 percent, and 15.5 percent for participants who had never drunk, drinkers who had up to 40 drink-years, and those with more than 40 drink-years, respectively ($p=0.007$). Participants exposed to degreasing chemicals had a higher mean ALT than those not exposed (21.0 U/L vs. 20.1 U/L, $p=0.032$).

For the adjusted continuous analysis, a significant group-by-lifetime alcohol history interaction was found ($p=0.020$). Other significant covariates in the model were age ($p<0.001$), current alcohol use-by-race ($p<0.001$), current alcohol use-by-industrial chemical exposure ($p=0.011$), and industrial chemical exposure-by-degreasing chemical exposure ($p=0.038$). Lifetime alcohol history was categorized to explore the interaction with group. Table J-3 presents adjusted mean ALT levels by group for the three levels of lifetime alcohol history. The interaction can partly be explained by a marginally significant group difference for participants with greater than 40 lifetime drink-years ($p=0.095$). Of the three lifetime alcohol history categories, the Ranch Hand adjusted mean was highest for this category (21.8 U/L) in contrast to the Comparison adjusted mean, which was lowest (20.3 U/L). Also, the Comparison adjusted means decreased as lifetime drinking increased. This pattern contrasted with the Ranch Hand group, which showed the lowest adjusted mean for moderate drinkers and higher adjusted means for the other categories. Because the statistical significance of the group-by-lifetime alcohol history interaction was greater than 0.01, an additional adjusted analysis was done to assess the overall group difference. This analysis excluded the group-by-

lifetime alcohol history interaction. The group difference was not significant (p=0.915) after adjusting for the covariates discussed above.

The adjusted relative risk was not significant for the discrete analysis (p=0.313). Three pairwise covariate interactions were used for adjustment (age-by-occupation, p=0.003; age-by-industrial chemical exposure, p=0.009; and current alcohol use-by-industrial chemical exposure, p=0.031).

GGT

Neither the GGT mean level nor the percentage of abnormal GGT values was significantly different between groups (p=0.552 and p=0.834, respectively) in unadjusted analyses.

Using pooled group data, significant associations with race, current alcohol use, and lifetime alcohol history were found, along with marginal associations with occupation and degreasing chemical exposure. The GGT mean was much larger for Blacks than nonblacks (44.1 U/L vs. 32.3 U/L, respectively; p<0.001), as was the percentage of abnormal values (14.9% abnormal vs. 7.8% abnormal, respectively; p=0.011). GGT was highly correlated with current alcohol use (r=0.271, p<0.001), and the percentage of abnormal values steadily increased with drinking (5.6%, 16.5%, and 28.8% for participants currently drinking ≤1 drinks/day, >1-4 drinks/day, and >4 drinks/day, respectively; p<0.001). The correlation with lifetime alcohol history was 0.110 (p<0.001). As with AST and ALT, the percentage of abnormal values was highest for heavy drinkers (14.9% for participants with more than 40 drink-years), less for individuals who had never drunk (7.8%), and lowest for the middle lifetime alcohol history category (6.0% for >0-40 drink-years, p<0.001). Relatively more abnormal levels were seen for the enlisted flyers than for the other occupational cohorts (7.8% abnormal for officers, 11.1% abnormal for enlisted flyers, and 7.6% abnormal for enlisted groundcrew; p=0.089). The mean for participants exposed to degreasing chemicals, 33.6 U/L, was larger than the mean for those not exposed, 31.9 U/L (p=0.068).

No significant group differences were found in the adjusted continuous (p=0.365) and discrete (p=0.695) analyses. The continuous model was adjusted for race (p<0.001), degreasing chemical exposure (p=0.022), and a current alcohol use-by-lifetime alcohol history interaction (p<0.001). Covariates used for adjustment in the discrete analysis were an occupation-by-degreasing chemical exposure interaction (p=0.043), a race-by-degreasing chemical exposure interaction (p=0.038), and a current alcohol use-by-lifetime alcohol history interaction (p=0.028).

Alkaline Phosphatase

For the unadjusted continuous analysis, the Ranch Hand group alkaline phosphatase mean, 93.7 U/L, was significantly higher than the Comparison group mean, 90.3 U/L (p<0.001). In contrast, the discrete analysis was not significant (p=0.999).

Significant covariate associations were found with occupation, current wine use, lifetime wine history, industrial chemical exposure, and degreasing

chemical exposure. A marginally significant association was found with age. The occupational effect ($p<0.001$) showed a much higher mean level for enlisted flyers, 95.6 U/L, than for officers, 87.6 U/L. The enlisted groundcrew mean, 93.9 U/L, fell in between. After categorizing alkaline phosphatase, the percentage of abnormalities was lowest for officers, 3.5 percent; higher for enlisted flyers, 5.5 percent; and highest for enlisted groundcrew, 5.7 percent. This relationship was marginally significant ($p=0.059$). A strong negative association with current wine use was noted at the 1985 followup analysis and was explored further in this study. Both wine-related variables were negatively correlated with alkaline phosphatase ($r=-0.048$, $p=0.023$, for current wine use; $r=-0.071$, $p<0.001$, for lifetime wine history). These findings were opposite of expectation. The percentage of abnormal values was higher for participants who do not currently drink wine than for current wine drinkers (5.9% vs. 3.4%, $p=0.006$). Men who had never drunk wine had relatively more abnormal levels than moderate and heavy wine drinkers (6.3%, 3.5%, and 2.1% for 0 drink-years of wine, >0-10 drink-years of wine, and >10 drink-years of wine, respectively; $p=0.005$). The alkaline phosphatase mean for individuals exposed to industrial chemicals was larger than for those not exposed (93.1 U/L vs. 90.1 U/L, $p=0.001$). Similarly, the percentage of abnormal values was significantly higher (5.9% vs. 3.5%, respectively; $p=0.010$). Participants exposed to degreasing chemicals had a higher mean, 92.5 U/L, than those not exposed, 90.6 U/L ($p=0.050$); the percentage of abnormalities was marginally significantly higher (5.5% vs. 3.9%, respectively; $p=0.096$). A positive correlation with age ($r=0.040$, $p=0.054$) was found.

The results of the adjusted analyses supported the unadjusted analyses. A highly significant group difference was found in the continuous analysis ($p<0.001$), but the adjusted relative risk was not significant for the discrete analysis ($p=0.892$). Age ($p<0.001$), lifetime wine history ($p=0.028$), occupation-by-current wine use ($p=0.007$), and race-by-industrial chemical exposure ($p=0.006$) were used for adjustment in the continuous analysis. The discrete model was adjusted for age ($p<0.001$), industrial chemical exposure ($p=0.003$), and lifetime wine history ($p=0.013$).

Total Bilirubin

No significant group difference was found for total bilirubin in either the unadjusted continuous ($p=0.611$) or discrete ($p=0.292$) analyses.

Treating total bilirubin as a continuous variable, significant associations with age ($p=0.042$) and occupation ($p=0.035$) were found, along with a marginally significant association with current alcohol use ($p=0.092$). No covariates were significantly associated after categorizing total bilirubin; industrial chemical exposure showed a marginal effect ($p=0.069$). A positive correlation with age was seen ($r=0.043$), and officers had a larger mean, 0.80 mg/dl, than either enlisted groundcrew (0.77 mg/dl) or enlisted flyers (0.77 mg/dl). The correlation with current alcohol use was 0.035. Participants exposed to industrial chemicals had a higher percentage of abnormal total bilirubin levels than participants not exposed (4.0% vs. 2.5%, respectively).

The group difference was not significant for the adjusted continuous analysis ($p=0.622$). An age-by-industrial chemical exposure interaction

(p=0.032) and a current alcohol use-by-lifetime alcohol history interaction (p=0.023) were used for adjustment. Group interactions with both alcohol-related variables were found for the adjusted discrete analysis (group-by-current alcohol use, p=0.036; group-by-lifetime alcohol history, p=0.040). To investigate these interactions, unadjusted relative risks were derived for each of six current alcohol use-by-lifetime alcohol history covariate stratum. As seen in Table J-3, none of these relative risks were significantly different from one. After excluding the interactions, no significant group difference was found (p=0.237). No covariates were used for adjustment in this analysis.

Direct Bilirubin

The results of the unadjusted continuous and discrete analyses showed no significant group differences for direct bilirubin (p=0.969 and p=0.342, respectively).

Of the candidate covariates, only occupation was significantly associated with direct bilirubin; current alcohol use was marginally associated. Although both the continuous and discrete tests of association showed an effect due to occupation, the pattern of the relationship was inconsistent. Officers had the largest mean, 0.17 mg/dl, followed by enlisted groundcrew, 0.16 mg/dl, and enlisted flyers, 0.15 mg/dl (p=0.022). In contrast, the highest percentage of abnormal values was found for enlisted flyers, 6.1 percent, followed by officers, 4.2 percent, and enlisted groundcrew, 3.2 percent (p=0.054). The correlation between direct bilirubin and current alcohol use was 0.040 (p=0.059). The percentages of abnormal values were 3.7%, 6.1%, and 2.7% for men who currently had no more than one drink per day, those who had more than one but at most four drinks per day, and those who daily consumed more than four drinks, respectively (p=0.074).

A significant group-by-race interaction was found for the adjusted continuous analysis (p=0.022). The only significant covariate included for adjustment was occupation (p=0.029). Exploration of the interaction showed no significant group difference for nonblacks (p=0.565), but revealed a significantly higher adjusted mean for Black Ranch Hands than for Black Comparisons (0.181 mg/dl vs. 0.134 mg/dl, respectively; p=0.026). A further adjusted analysis was done ignoring the group-by-race interaction. Adjusting for occupation (p=0.023), the result for this analysis found no significant difference between groups (p=0.985).

The adjusted discrete analysis detected a highly significant group-by-degreasing chemical exposure interaction (p=0.009). Occupation (p=0.044) was included for adjustment. Ranch Hands who had been exposed to degreasing chemicals had significantly fewer abnormal direct bilirubin levels than Comparisons who had been exposed (Adj. RR: 0.48, 95% C.I.: [0.27,0.87], p=0.016). Conversely, the relative risk for Ranch Hands who never had been exposed to degreasing chemicals was greater than one, but not significant (Adj. RR: 1.59, 95% C.I.: [0.81,3.14], p=0.180).

LDH

The Ranch Hand group LDH mean and percentage of abnormal values were not significantly different from the Comparison group mean and percentage of abnormalities for the unadjusted analyses (p=0.692 and p=0.999, respectively).

Using pooled group data, a significant positive correlation between LDH and age was found (r=0.102, p<0.001). Current alcohol use (p=0.058) and lifetime alcohol history (p=0.031) were also associated with LDH, after categorization. For both alcohol-related variables, the percentage of abnormalities increased with drinking (1.1%, 1.5%, and 4.1% for the ≤1 drink/day, >1-4 drinks/day, and the >4 drinks/day categories, respectively; and 0.5%, 1.0%, and 2.4% for the 0 drink-years, >0-40 drink-years, and the >40 drink-years categories, respectively).

Both the adjusted continuous and discrete analyses showed no significant group difference (p=0.804 and p=0.954, respectively). The continuous analysis was adjusted for age-by-occupation (p=0.025) and current alcohol use-by-lifetime alcohol history (p=0.025). No covariates were included for adjustment in the discrete analysis.

Cholesterol

No significant group differences were found for cholesterol for either the continuous or the discrete analysis (p=0.379 and p=0.179, respectively) without adjustment for covariates.

The covariate tests of association showed significant relationships between cholesterol and age, occupation, current alcohol use, and industrial chemical exposure. The correlation with age was 0.079 (p<0.001). Participants born between 1923 and 1941 had a higher percentage of abnormal values, 15.0 percent, than those born in or before 1922, 10.7 percent, and those born in or after 1942, 11.0 percent (p=0.018). For occupation (p=0.012), enlisted flyers had a larger mean (219.5 mg/dl) than officers (212.8 mg/dl) and enlisted groundcrew (213.0 mg/dl). This pattern was also evident in the discrete analysis, where 17.4 percent of enlisted flyers had abnormal values, in contrast to 12.1 percent and 12.5 percent of officers and enlisted groundcrew, respectively (p=0.028). Current alcohol use was positively correlated with cholesterol (r=0.048, p=0.023); the percentage of abnormal values increased with drinking (12.7%, 13.7%, and 21.9% for the ≤1 drinks/day, >1-4 drinks/day, and >4 drinks/day categories, respectively; p=0.068). The mean for individuals exposed to industrial chemicals was higher than for those not exposed (215.6 mg/dl vs. 212.0 mg/dl, respectively; p=0.030).

Group differences in cholesterol remained nonsignificant after covariate adjustment for both the continuous analysis (p=0.437) and the discrete analysis (p=0.177). Age (p<0.001), current alcohol use (p=0.021), industrial chemical exposure (p=0.023), and an occupation-by-race interaction (p=0.003) were used for adjustment in the continuous analysis. The discrete analysis was adjusted for age (p=0.048) and occupation (p=0.034).

HDL

No significant group differences were found for HDL for either the unadjusted continuous or discrete analyses ($p=0.847$ and $p=0.992$, respectively).

The covariate tests of association showed significant relationships between HDL and race, occupation, current alcohol use, lifetime alcohol history, industrial chemical exposure, and degreasing chemical exposure. Dichotomized HDL was significantly associated with degreasing chemical exposure. The HDL mean changed significantly with race ($p<0.001$); the HDL mean among Blacks was 51.13 mg/dl and the mean among nonblacks was 46.69 mg/dl. For occupation ($p<0.001$), officers had a higher HDL mean (48.23 mg/dl) than enlisted flyers (46.13 mg/dl) or enlisted groundcrew (46.18 mg/dl). Current alcohol use was positively associated with HDL ($p<0.001$), with the HDL means for light, moderate, and heavy drinkers being 45.50 mg/dl, 51.35 mg/dl, and 58.71 mg/dl, respectively. For lifetime alcohol history ($p<0.001$), the HDL means for never, moderate, and heavy drinkers were 43.85 mg/dl, 46.62 mg/dl, and 49.14 mg/dl, respectively. The mean HDL for participants reporting exposure to industrial chemicals (46.45 mg/dl) was significantly less ($p=0.029$) than the mean HDL for participants not exposed to industrial chemicals (47.56 mg/dl). The dichotomized HDL was significantly associated with degreasing chemical exposure ($p=0.037$); 1.3 percent of participants who reported exposure and 0.4 percent of participants who reported no exposure had HDL below 25 mg/dl.

A significant group-by-lifetime alcohol history interaction was found for the adjusted continuous analysis of HDL ($p=0.036$). Occupation ($p=0.042$), current alcohol use ($p=0.001$), a race-by-degreasing chemical interaction ($p=0.004$), a current alcohol use-by-lifetime alcohol history interaction ($p<0.001$), and a race-by-industrial chemical exposure interaction ($p=0.042$) were used for adjustment. Results were derived for each level of lifetime alcohol history to explore the interaction. The Ranch Hand HDL means among never, moderate, and heavy drinkers with reference to lifetime alcohol history, were 47.23 mg/dl, 49.60 mg/dl, and 47.41 mg/dl, respectively; the corresponding Comparison HDL means were 47.58 mg/dl, 48.84 mg/dl, and 49.33 mg/dl. The difference between Ranch Hands and Comparisons for heavy drinkers was marginally significant ($p=0.067$). The adjusted group means were not significantly different ($p=0.648$) after excluding the group-by-lifetime alcohol history interaction.

No significant group difference was found for the adjusted discrete analysis of HDL ($p=0.999$). Degreasing chemical exposure was the only covariate used for adjustment ($p=0.040$).

Cholesterol-HDL Ratio

No significant group differences were found for cholesterol-HDL ratio for either the unadjusted continuous or discrete analyses ($p=0.357$ and $p=0.348$, respectively).

The covariate tests of association showed significant relationships between the continuously distributed cholesterol-HDL ratio and age, race,

occupation, current alcohol use, lifetime alcohol history, industrial chemical exposure, and degreasing chemical exposure. The discretized cholesterol-HDL ratio was significantly associated with race, occupation, current alcohol use, and degreasing chemical exposure. The cholesterol-HDL ratio mean changed significantly with age ($p=0.009$); the cholesterol-HDL ratio means among participants born in or after 1942, between 1923 and 1941, and in or before 1922 were 4.80, 4.99, and 4.84, respectively. The cholesterol-HDL ratio mean for Blacks (4.51) was significantly different from the cholesterol-HDL ratio mean for nonblacks (4.93) ($p=0.001$).

For occupation, the officer, enlisted flyer, and enlisted groundcrew cholesterol-HDL ratio means (4.73, 5.13, and 4.96, respectively) were significantly different ($p<0.001$). The cholesterol-HDL ratio mean changed significantly with current alcohol use ($p<0.001$); the cholesterol-HDL ratio means for light, moderate, and heavy drinkers were 5.00, 4.60, and 4.16, respectively. The cholesterol-HDL ratio mean also changed significantly with lifetime alcohol history ($p=0.003$); the cholesterol-HDL ratio means for never, moderate, and heavy drinkers were 5.13, 4.93, and 4.75, respectively. The cholesterol-HDL ratio means changed significantly with industrial chemical exposure ($p=0.002$); the cholesterol-HDL ratio mean among participants who reported industrial chemical exposure was 4.99 and the mean among those who reported no exposure was 4.80. The cholesterol-HDL ratio means also changed significantly with degreasing chemical exposure ($p<0.001$); the cholesterol-HDL ratio mean among participants who reported degreasing chemical exposure was 5.00 and the mean among those who reported no exposure was 4.76.

The dichotomized cholesterol-HDL ratio was significantly associated with race ($p=0.045$); a greater percentage of nonblacks had abnormalities (43.2%) than Blacks (34.3%). There was a significant association between cholesterol-HDL ratio and occupation ($p=0.002$); the percentages of participants with cholesterol-HDL ratio abnormalities among officers, enlisted flyers, and enlisted groundcrew were 38.5 percent, 48.4 percent, and 44.0 percent, respectively. There was also a significant association between the dichotomized cholesterol-HDL ratio and current alcohol use ($p<0.001$); the percentages of participants with cholesterol-HDL ratio abnormalities for light, moderate, and heavy drinkers were 45.4 percent, 35.0 percent, and 16.4 percent, respectively. There was a significant association between the dichotomized cholesterol-HDL ratio and degreasing chemical exposure ($p=0.008$); 44.9 percent of participants who reported exposure, and 39.3 percent of participants who reported no exposure to degreasing chemicals had cholesterol-HDL ratio abnormalities.

Group differences in the cholesterol-HDL ratio remained nonsignificant after adjustment for covariates in both the continuous analysis ($p=0.509$) and the discrete analysis ($p=0.434$). Current alcohol use ($p=0.002$), a race-by-degreasing chemical exposure interaction ($p=0.017$), an age-by-lifetime alcohol history interaction ($p=0.040$), and a current alcohol use-by-lifetime alcohol history interaction ($p=0.004$) contributed to the continuous model. The discrete analysis was adjusted for age ($p=0.038$), rece ($p=0.036$), occupation ($p<0.001$), and current alcohol use ($p<0.001$).

Triglycerides

Group differences for triglycerides were not significant for both the unadjusted continuous (p=0.355) and discrete (p=0.248) analyses.

Treating triglycerides as a continuous variable, significant covariate associations were found with age (p=0.009), race (p<0.001), occupation (p=0.003), industrial chemical exposure (p=0.027), and degreasing chemical exposure (p<0.001). After categorizing triglycerides, no significant covariate associations were found. The correlation with age was 0.055. Non-blacks had a much higher mean, 119.3 mg/dl, than did Blacks, 96.1 mg/dl. For occupation, enlisted flyers had the highest mean, 126.5 mg/dl, followed by enlisted groundcrew, 119.9 mg/dl, and officers, 111.7 mg/dl. The mean for participants exposed to industrial chemicals (121.0 mg/dl) was larger than for those not exposed (114.0 mg/dl), and the mean for individuals exposed to degreasing chemicals was larger than the mean for those not exposed (122.7 mg/dl vs. 110.7 mg/dl, respectively).

The results of the adjusted analyses and triglycerides did not show a significant group difference (p=0.459 and p=0.172 for the continuous and discrete analysis, respectively). Significant covariates used to adjust the continuous model were age (p<0.001), occupation (p=0.001), degreasing chemical exposure (p=0.009), and a race-by-lifetime alcohol history interaction (p=0.038). Race (p=0.039) and current alcohol use-by-lifetime alcohol history (p=0.043) were used for the adjusted discrete analysis.

Creatine Kinase

No significant group differences were found for creatine kinase for either the unadjusted continuous (p=0.611) or the discrete (p=0.114) analyses.

Examining the relationship with the covariates revealed an extremely large creatine kinase difference between races that was highly significant (p<0.001, continuous and discrete), and a strong association with age (p<0.001). A marginally significant negative association with lifetime alcohol history was also noted (p=0.055). The mean for Blacks, 197.5 U/L, was nearly twice as large as the mean for nonblacks, 105.4 U/L. This finding was supported by the discrete test of association, in which 34.3 percent of Blacks had abnormal values, versus only 5.1 percent of nonblacks. Age was negatively correlated with creatine kinase (r=-0.074). The correlation with lifetime alcohol history was -0.040.

Group differences in creatine kinase were not significant for the adjusted continuous analysis (p=0.500) and the discrete analysis (p=0.122), supporting the unadjusted results. The continuous model was adjusted for age (p=0.002), race (p<0.001), and current alcohol use-by occupation (p=0.045). Race (p<0.001) and an age-by-degreasing chemical exposure interaction (p=0.019) were included in the final adjusted discrete model.

Fasting Glucose

No significant differences were found between groups in the unadjusted continuous or discrete analyses for fasting glucose (p=0.504 and p=0.606, respectively).

Age was highly correlated with fasting glucose (r=0.195, p<0.001). The percentage of abnormal values increased with age (5.3% for participants born in or after 1942, 17.4% for those born between 1923 and 1941, and 25.0% for those born in or before 1922). The correlation with lifetime alcohol history was 0.067 (p=0.002). The percentages of abnormal values were 13.2 percent, 9.9 percent, and 20.7 percent for never, moderate, and heavy drinkers, respectively (p<0.001).

Group differences in fasting glucose were not significant for the adjusted continuous (p=0.534) and the discrete analysis (p=0.565). Significant covariates included in the continuous analysis were age-by-race (p=0.002), race-by-lifetime alcohol history (p=0.050), and occupation-by-lifetime alcohol history (p<0.001). The discrete analysis included age (p<0.001), race (p=0.008), lifetime alcohol history (p=0.021), and degreasing chemical exposure (p=0.024) for adjustment.

Exposure Index Analysis

Laboratory Examination Variables

Exposure index analyses were done for all 13 laboratory examination variables. Each variable was analyzed in both continuous and discrete forms. Unadjusted and adjusted results are presented in Tables 13-8 and 13-9, respectively. Many exposure index-by-covariate interactions were detected in the adjusted analyses, particularly for the discrete analyses. These interactions are listed in Table 13-10, and stratified results are presented in Table J-4. In several instances, meaningful interpretation of the interaction was obscured because the cell sizes were very small after stratification.

Both the statistical significance of the results and whether trends in the data supported a herbicide effect were investigated. Examination of Table 13-8 shows that many variables exhibited increasing dose-response relationships, without a significant result. Of the 39 unadjusted continuous analyses for the three occupational cohorts, the means for 14 analyses exhibited increasing dose-response patterns. However, the overall result was not significant for any of these analyses. The means for five analyses decreased with the exposure index categories, also without a statistically significant finding. Breaking this down by occupation showed that the means for officers increased with exposure level for five variables (AST, ALT, GGT, alkaline phosphatase, and triglycerides) and decreased for HDL; the enlisted flyer means for GGT and direct bilirubin increased and the mean for alkaline phosphatase and HDL decreased; and the enlisted groundcrew means increased with exposure level for seven variables (AST, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, cholesterol, and HDL) and decreased for two variables (GGT and fasting glucose). Trends such as these are discussed in Chapter 21.

TABLE 13-8.

Unadjusted Exposure Index for Hepatic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
AST	Officer	n	128	124	122	Overall		0.429
		Mean[a]	25.4	26.1	26.7	M vs. L	--	0.450
		95% C.I.[a]	(24.3,26.5)	(24.6,27.6)	(25.0,28.6)	H vs. L	--	0.196
		Number/%				Overall		0.086
		High	4 3.1%	5 4.0%	11 9.0%	M vs. L	1.30 (0.34,4.97)	0.960
		Normal	124 96.9%	119 96.0%	111 91.0%	H vs. L	3.07 (0.95,9.93)	0.088
	Enlisted Flyer	n	55	63	53	Overall		0.898
		Mean[a]	24.8	24.4	25.0	M vs. L	--	0.778
		95% C.I.[a]	(22.9,26.8)	(22.5,26.4)	(23.4,26.7)	H vs. L	--	0.873
		Number/%				Overall		0.552
		High	1 1.8%	3 4.8%	1 1.9%	M vs. L	2.70 (0.27,26.74)	0.724
		Normal	54 98.2%	60 95.2%	52 98.1%	H vs. L	1.04 (0.06,17.04)	0.999
	Enlisted Groundcrew	n	146	155	140	Overall		0.524
		Mean[a]	25.5	25.8	26.6	M vs. L	--	0.790
		95% C.I.[a]	(24.4,26.7)	(24.4,27.2)	(25.2,28.1)	H vs. L	--	0.255
		Number/%				Overall		0.226
		High	5 3.4%	7 4.5%	11 7.9%	M vs. L	1.33 (0.41,4.30)	0.854
		Normal	141 96.6%	148 95.5%	129 92.1%	H vs. L	2.41 (0.81,7.11)	0.168

TABLE 13-8. (continued)

Unadjusted Exposure Index for Hepatic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
ALT	Officer	n	128	124	122	Overall		0.592
		Mean[a]	20.1	20.4	21.4	M vs. L	--	0.812
		95% C.I.[a]	(18.6,21.7)	(18.6,22.3)	(25.0,28.6)	H vs. L	--	0.325
		Number/%				Overall		0.783
		High	14 10.9%	17 13.7%	16 13.1%	M vs. L	1.29 (0.61,2.75)	0.632
		Normal	114 89.1%	107 86.3%	106 86.9%	H vs. L	1.23 (0.57,2.64)	0.738
	Enlisted Flyer	n	55	63	53	Overall		0.394
		Mean[a]	18.6	20.7	20.5	M vs. L	--	0.211
		95% C.I.[a]	(16.6,20.8)	(18.3,23.4)	(18.2,23.1)	H vs. L	--	0.259
		Number/%				Overall		0.775
		High	4 7.3%	7 11.1%	5 9.4%	M vs. L	1.59 (0.44,5.77)	0.696
		Normal	51 92.7%	56 88.9%	48 90.6%	H vs. L	1.33 (0.34,5.24)	0.952
	Enlisted Groundcrew	n	146	155	140	Overall		0.368
		Mean[a]	20.2	21.7	20.3	M vs. L	--	0.207
		95% C.I.[a]	(18.8,21.8)	(20.0,23.6)	(18.6,22.1)	H vs. L	--	0.967
		Number/%				Overall		0.301
		High	15 10.3%	25 16.1%	17 12.1%	M vs. L	1.68 (0.85,3.33)	0.184
		Normal	131 89.7%	130 83.9%	123 87.9%	H vs. L	1.21 (0.58,2.52)	0.754

TABLE 13-8. (continued)

Unadjusted Exposure Index for Hepatic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
GGT	Officer	n	128	124	122	Overall		0.140
		Mean[a]	30.9	31.4	36.2	M vs. L	--	0.839
		95% C.I.[a]	(27.7,34.4)	(27.9,35.3)	(31.6,41.4)	H vs. L	--	0.076
		Number/%				Overall		0.018
		High	7 5.5%	8 6.5%	18 14.8%	M vs. L	1.19 (0.42,3.39)	0.948
		Normal	121 94.5%	116 93.5%	104 85.2%	H vs. L	2.99 (1.20,7.44)	0.024
	Enlisted Flyer	n	55	63	53	Overall		0.875
		Mean[a]	32.5	34.1	34.7	M vs. L	--	0.720
		95% C.I.[a]	(26.1,40.5)	(29.2,39.9)	(29.5,40.8)	H vs. L	--	0.637
		Number/%				Overall		0.681
		High	7 12.7%	5 7.9%	6 11.3%	M vs. L	0.59 (0.18,1.98)	0.578
		Normal	48 87.3%	58 92.1%	47 88.7%	H vs. L	0.88 (0.27,2.80)	0.999
	Enlisted Groundcrew	n	146	155	140	Overall		0.760
		Mean[a]	34.0	33.8	32.3	M vs. L	--	0.932
		95% C.I.[a]	(30.5,37.9)	(30.7,37.3)	(28.8,36.1)	H vs. L	--	0.510
		Number/%				Overall		0.461
		High	8 5.5%	11 7.1%	13 9.3%	M vs. L	1.32 (0.52,3.37)	0.736
		Normal	138 94.5%	144 92.9%	127 90.7%	H vs. L	1.77 (0.71,4.40)	0.314

TABLE 13-8. (continued)

Unadjusted Exposure Index for Hepatic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Alkaline Phosphatase	Officer	n	128	124	122	Overall		0.302
		Mean[a]	87.9	88.9	92.0	M vs. L	--	0.699
		95% C.I.[a]	(84.5,91.4)	(84.8,93.2)	(88.3,95.9)	H vs. L	--	0.115
		Number/%				Overall		0.117
		High	2 1.6%	8 6.5%	4 3.3%	M vs. L	4.35 (0.90,20.88)	0.092
		Normal	126 98.4%	116 93.5%	118 96.7%	H vs. L	2.14 (0.38,11.88)	0.638
	Enlisted Flyer	n	55	63	53	Overall		0.334
		Mean[a]	99.4	96.0	92.2	M vs. L	--	0.505
		95% C.I.[a]	(91.3,108.3)	(90.8,101.5)	(86.3,98.4)	H vs. L	--	0.170
		Number/%				Overall		0.702
		High	2 3.6%	3 4.8%	1 1.9%	M vs. L	1.33 (0.21,8.24)	0.999
		Normal	53 96.4%	60 95.2%	52 98.1%	H vs. L	0.51 (0.05,5.79)	0.999
	Enlisted Groundcrew	n	146	155	140	Overall		0.241
		Mean[a]	94.1	97.2	98.3	M vs. L	--	0.201
		95% C.I.[a]	(90.7,97.6)	(94.0,100.6)	(94.4,102.3)	H vs. L	--	0.117
		Number/%				Overall		0.994
		High	9 6.2%	10 6.5%	9 6.4%	M vs. L	1.05 (0.41,2.66)	0.999
		Normal	137 93.8%	145 93.5%	131 93.6%	H vs. L	1.05 (0.40,2.72)	0.999

TABLE 13-8. (continued)

Unadjusted Exposure Index for Hepatic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Total Bilirubin	Officer	n	128	124	122	Overall		0.415
		Mean[b]	0.805	0.776	0.815	M vs. L	--	0.315
		95% C.I.[b]	(0.766, 0.844)	(0.739, 0.815)	(0.769, 0.863)	H vs. L	--	0.740
		Number/%				Overall		0.694
		High	3 2.3%	2 1.6%	4 3.3%	M vs. L	0.68 (0.11,4.16)	0.999
		Normal	125 97.7%	122 98.4%	118 96.7%	H vs. L	1.41 (0.31,6.45)	0.999
	Enlisted Flyer	n	55	63	53	Overall		0.195
		Mean[b]	0.744	0.735	0.809	M vs. L	--	0.813
		95% C.I.[b]	(0.692, 0.800)	(0.678, 0.796)	(0.745, 0.876)	H vs. L	--	0.139
		Number/%				Overall		0.552
		High	1 1.8%	3 4.8%	1 1.9%	M vs. L	2.70 (0.27,26.74)	0.724
		Normal	54 98.2%	60 95.2%	52 98.1%	H vs. L	1.04 (0.06,17.04)	0.999
	Enlisted Groundcrew	n	146	155	140	Overall		0.382
		Mean[b]	0.753	0.773	0.791	M vs. L	--	0.434
		95% C.I.[b]	(0.718, 0.789)	(0.737, 0.811)	(0.751, 0.833)	H vs. L	--	0.164
		Number/%				Overall		0.664
		High	2 1.4%	3 1.9%	1 0.7%	M vs. L	1.42 (0.23,8.63)	0.999
		Normal	144 98.6%	152 98.1%	139 99.3%	H vs. L	0.52 (0.05,5.78)	0.999

TABLE 13-8. (continued)

Unadjusted Exposure Index for Hepatic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Direct Bilirubin	Officer	n	128	124	122	Overall		0.191
		Mean[b]	0.176	0.150	0.169	M vs. L	--	0.055
		95% C.I.[b]	(0.157, 0.196)	(0.132, 0.169)	(0.145, 0.195)	H vs. L	--	0.641
		Number/%				Overall		0.010
		High	4 3.1%	1 0.8%	10 8.2%	M vs. L	0.25 (0.03,2.29)	0.390
		Normal	124 96.9%	123 99.2%	112 91.8%	H vs. L	2.77 (0.84,9.07)	0.140
	Enlisted Flyer	n	55	63	53	Overall		0.598
		Mean[b]	0.134	0.145	0.156	M vs. L	--	0.565
		95% C.I.[b]	(0.109, 0.116)	(0.118, 0.175)	(0.122, 0.195)	H vs. L	--	0.315
		Number/%				Overall		0.609
		High	2 3.6%	5 7.9%	3 5.7%	M vs. L	2.28 (0.43,12.28)	0.548
		Normal	53 96.4%	58 92.1%	50 94.3%	H vs. L	1.59 (0.26,9.92)	0.964
	Enlisted Groundcrew	n	146	155	140	Overall		0.085
		Mean[b]	0.141	0.163	0.168	M vs. L	--	0.089
		95% C.I.[b]	(0.124, 0.160)	(0.146, 0.181)	(0.151, 0.187)	H vs. L	--	0.041
		Number/%				Overall		0.719
		High	4 2.7%	4 2.6%	2 1.4%	M vs. L	0.94 (0.23,3.83)	0.999
		Normal	142 97.3%	151 97.4%	138 98.6%	H vs. L	0.51 (0.09,2.86)	0.724

TABLE 13-8. (continued)

Unadjusted Exposure Index for Hepatic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
LDH	Officer	n	128	124	122	Overall		0.780
		Mean[a]	127.3	128.9	127.1	M vs. L	--	0.563
		95% C.I.[a]	(124.1, 130.6)	(124.8, 133.1)	(123.4, 131.0)	H vs. L	--	0.950
		Number/%				Overall		0.859
		High	2 1.6%	3 2.4%	2 1.6%	M vs. L	1.56 (0.26,9.51)	0.970
		Normal	126 98.4%	121 97.6%	120 98.4%	H vs. L	1.05 (0.15,7.57)	0.999
	Enlisted Flyer	n	55	63	53	Overall		0.082
		Mean[a]	128.7	120.8	128.8	M vs. L	--	0.042
		95% C.I.[a]	(123.2, 134.5)	(115.9, 125.9)	(122.0, 136.0)	H vs. L	--	0.987
		Number/%				Overall		0.346
		High	1 1.8%	0 0.0%	0 0.0%	M vs. L	--[c]	0.932
		Normal	54 98.2%	63 100.0%	53 100.0%	H vs. L	--[c]	0.999
	Enlisted Groundcrew	n	146	155	140	Overall		0.245
		Mean[a]	127.8	128.6	131.7	M vs. L	--	0.726
		95% C.I.[a]	(124.8, 130.9)	(125.2, 132.1)	(128.2, 135.3)	H vs. L	--	0.099
		Number/%				Overall		0.769
		High	2 1.4%	1 0.7%	1 0.7%	M vs. L	0.47 (0.04,5.21)	0.956
		Normal	144 98.6%	154 99.3%	139 99.3%	H vs. L	0.52 (0.05,5.78)	0.999

TABLE 13-8. (continued)

Unadjusted Exposure Index for Hepatic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
Cholesterol	Officer	n	128	124	122	Overall		0.063
		Mean[a]	220.5	209.9	210.1	M vs. L	--	0.043
		95% C.I.[a]	(213.0, 228.4)	(203.2, 216.8)	(203.3, 217.1)	H vs. L	--	0.049
		Number/%				Overall		0.215
		High	22 17.2%	12 9.7%	18 14.8%	M vs. L	0.52 (0.24,1.10)	0.118
		Normal	106 82.8%	112 90.3%	104 85.2%	H vs. L	0.83 (0.42,1.65)	0.726
	Enlisted Flyer	n	55	63	53	Overall		0.509
		Mean[a]	219.7	212.8	221.4	M vs. L	--	0.388
		95% C.I.[a]	(207.8, 232.4)	(203.0, 223.1)	(210.4, 233.1)	H vs. L	--	0.843
		Number/%				Overall		0.762
		High	11 20.0%	10 15.9%	8 15.1%	M vs. L	0.76 (0.29,1.94)	0.730
		Normal	44 80.0%	53 84.1%	45 84.9%	H vs. L	0.71 (0.26,1.94)	0.678
	Enlisted Groundcrew	n	146	155	140	Overall		0.491
		Mean[a]	213.3	213.4	217.9	M vs. L	--	0.996
		95% C.I.[a]	(207.9, 219.0)	(207.7, 219.2)	(211.2, 225.0)	H vs. L	--	0.308
		Number/%				Overall		0.474
		High	17 11.6%	20 12.9%	23 16.4%	M vs. L	1.12 (0.56,2.24)	0.876
		Normal	129 88.4%	135 87.1%	117 83.6%	H vs. L	1.49 (0.76,2.93)	0.320

TABLE 13-8. (continued)

Unadjusted Exposure Index for Hepatic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	Est. Relative Risk (95% C.I.)	p-Value
HDL	Officer	n	128	124	122	Overall		0.151
		Mean	49.28	48.58	46.38	M vs. L	--	0.650
		95% C.I.	(47.15, 51.41)	(46.21, 50.95)	(44.31, 48.45)	H vs. L	--	0.062
		Number/%				Overall		0.593
		Low	0 0.0%	1 0.8%	1 0.8%	M vs. L	--[c]	0.309
		Normal	128 100.0%	123 99.2%	121 99.2%	H vs. L	--[c]	0.305
	Enlisted Flyer	n	55	63	53	Overall		0.700
		Mean	46.91	45.68	45.04	M vs. L	--	0.571
		95% C.I.	(43.16, 50.66)	(43.12, 48.24)	(42.02, 48.05)	H vs. L	--	0.408
		Number/%				Overall		0.127
		Low	1 1.8%	0 0.0%	3 5.7%	M vs. L	--[c]	0.282
		Normal	54 98.2%	63 100.0%	50 94.3%	H vs. L	--[c]	0.291
	Enlisted Groundcrew	n	146	155	140	Overall		0.882
		Mean	45.86	46.21	46.61	M vs. L	--	0.810
		95% C.I.	(43.79, 47.92)	(44.13, 48.28)	(44.49, 48.73)	H vs. L	--	0.616
		Number/%				Overall		0.395
		Low	0 0.0%	2 1.3%	1 0.7%	M vs. L	--[c]	0.168
		Normal	146 100.0%	153 98.7%	139 99.3%	H vs. L	--[c]	0.306