Table 13-78. Summary of Categorized Dioxin Analysis (Model 3) for Gastrointestinal Variables (Ranch Hands vs. Comparisons)

	UNADJUSTED			
Variable	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Medical Records				
Uncharacterized Hepatitis (D)	NS	ns	NS	NS
Jaundice (Unspecified) (D)	NS	-0.017	ns*	-0.001
Chronic Liver Disease and Cirrhosis (Alcohol-related) (D)	ns	NS	NS	NS
Chronic Liver Disease and Cirrhosis (Non-alcohol-related) (D)	NS	NS	NS	NS
Liver Abscess and Sequelae of Chronic Liver Disease (D)	ns	ns	NS	NS
Enlarged Liver (Hepatomegaly) (D)	ns	ns	NS	ns
Other Liver Disorders (D)	NS	NS	+0.009	+0.042
Physical Examination				
Current Hepatomegaly (D)	NS	NS	NS	NS
Laboratory				
AST (C)	ns	NS	NS	NS
AST (D)	ns	NS	NS*	NS*
ALT (C)	ns	NS	+0.027	+0.041
ALT (D)	ns	NS	+0.015	NS*
GGT (C)	ns	NS	+0.003	+0.007
GGT (D)	ns	NS	NS	NS*
Alkaline Phosphatase (C)	NS	NS*	NS	NS*
Alkaline Phosphatase (D)	NS	ns	NS	NS
Total Bilirubin (C)	NS	ns	ns	ns
Total Bilirubin (D)	ns	NS	ns	ns
Direct Bilirubin (D)	ns	--	--	--
Lactic Dehydrogenase (C)	NS	ns	NS	NS
Lactic Dehydrogenase (D)	NS	ns	ns	ns
Cholesterol (C)	ns	ns	+0.032	NS
Cholesterol (D)	ns	ns	+0.023	NS
HDL Cholesterol (C)[a]	NS	NS	ns	ns
HDL Cholesterol (D)	NS	NS	ns	NS
Cholesterol-HDL Ratio (C)	ns*	ns	+0.005	NS
Cholesterol-HDL Ratio (D)	ns	ns	+0.002	NS
Triglycerides (C)	ns	ns	+<0.001	+0.023
Triglycerides (D)	ns*	NS	+<0.001	+0.006
Creatine Phosphokinase (C)	NS	NS	NS	NS
Creatine Phosphokinase (D)	ns	ns	NS	ns
Serum Amylase (C)	ns	+0.019	ns	NS
Serum Amylase (D)	ns	NS	ns	NS
Antibodies for Hepatitis A (D)	ns	NS	NS	NS
Serological Evidence of Prior Hepatitis B Infection (D)	-<0.001	ns	ns	ns
Current Hepatitis B (D)	--	NS	--	NS
Antibodies for Hepatitis C (D)	ns	ns	ns	ns
Antibodies for Hepatitis D (D)	--	--	--	--
Stool Hemoccult (D)	ns	NS	ns	ns

Table 13-78. Summary of Categorized Dioxin Analysis (Model 3) for Gastrointestinal Variables (Ranch Hands vs. Comparisons) (Continued)

	UNADJUSTED			
Variable	**Background Ranch Hands vs. Comparisons**	**Low Ranch Hands vs. Comparisons**	**High Ranch Hands vs. Comparisons**	**Low plus High Ranch Hands vs. Comparisons**
Prealbumin (C)[a]	ns	ns	NS	ns
Prealbumin (D)	NS	ns	NS*	NS
Albumin (C)[a]	NS	ns*	NS	ns
Albumin (D)	ns	ns	ns	ns*
α-1-Acid Glycoprotein (C)	ns	NS	+0.045	NS
α-1-Acid Glycoprotein (D)	NS	NS	NS	NS
α-1-Antitrypsin (C)	NS	NS	+<0.001	+0.001
α-1-Antitrypsin (D):				
Low vs. Normal	NS	ns	ns	ns
High vs. Normal	NS	NS	NS	NS
α-2-Macroglobulin (C)	ns	ns	ns	ns
α-2-Macroglobulin (D)	ns*	ns	NS	ns
Apolipoprotein B (C)	ns*	ns	NS*	NS
Apolipoprotein B (D)	–0.017	ns	NS	ns
C3 Complement (C)[a]	ns	NS	+0.003	+0.013
C3 Complement (D)	NS	ns	ns	ns*
C4 Complement (C)[a]	ns	NS	NS	NS
C4 Complement (D)	NS	ns	ns	ns
Haptoglobin (C)	NS	NS*	+0.001	+0.001
Haptoglobin (D)	NS	NS	+0.023	+0.015
Transferrin (C)[a]	NS	NS	+0.010	+0.019
Transferrin (D)	ns	ns	–0.039	ns*

Note: NS or ns: Not significant (p>0.10).
NS* or ns*: Marginally significant (0.05<p≤0.10).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥1.00 for discrete analysis; difference of means nonnegative for continuous analysis.
–: Relative risk <1.00 for discrete analysis.
--: Analysis not performed because of the sparse number of participants with an abnormality.
[a] Negative difference considered adverse for this variable.

P-value given if p≤0.05.

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

	ADJUSTED			
Variable	**Background Ranch Hands vs. Comparisons**	**Low Ranch Hands vs. Comparisons**	**High Ranch Hands vs. Comparisons**	**Low plus High Ranch Hands vs. Comparisons**
Medical Records				
Uncharacterized Hepatitis (D)	NS	NS	NS	NS
Jaundice (Unspecified) (D)	ns	--	ns*	--
Chronic Liver Disease and Cirrhosis (Alcohol-related) (D)	NS	ns	ns	ns

Table 13-78. Summary of Categorized Dioxin Analysis (Model 3) for Gastrointestinal Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	ADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Chronic Liver Disease and Cirrhosis (Non-alcohol-related) (D)	NS	NS	NS	NS
Liver Abscess and Sequelae of Chronic Liver Disease (D)	--	--	NS	--
Enlarged Liver (Hepatomegaly) (D)	ns	ns	NS	ns
Other Liver Disorders (D)	NS	NS	+0.009	NS*
Physical Examination				
Current Hepatomegaly (D)	NS	NS	NS	NS
Laboratory				
AST (C)	ns	NS	NS	NS*
AST (D)	ns	NS	+0.024	+0.041
ALT (C)	ns	NS*	NS*	+0.026
ALT (D)	ns	NS	NS*	NS*
GGT (C)	ns	NS	+0.006	+0.006
GGT (D)	ns	NS	NS	NS*
Alkaline Phosphatase (C)	+0.008	NS*	ns	NS
Alkaline Phosphatase (D)	NS	ns	NS	NS
Total Bilirubin (C)	ns	ns	NS	NS
Total Bilirubin (D)	ns	NS	ns	ns
Direct Bilirubin (D)	NS	--	--	--
Lactic Dehydrogenase (C)	NS	ns	NS	NS
Lactic Dehydrogenase (D)	NS	ns	ns	ns
Cholesterol (C)	ns	ns	NS	NS
Cholesterol (D)	ns	NS	NS*	NS
HDL Cholesterol (C)[a]	NS	NS	NS	NS
HDL Cholesterol (D)	+0.049	NS	ns	ns
Cholesterol-HDL Ratio (C)	ns	ns	NS	NS
Cholesterol-HDL Ratio (D)	NS	ns	NS	NS
Triglycerides (C)	ns	NS	+0.013	NS*
Triglycerides (D)	ns	NS	+0.009	+0.012
Creatine Phosphokinase (C)	ns	NS	NS	NS
Creatine Phosphokinase (D)	ns	ns	NS	ns
Serum Amylase (C)	ns	NS*	ns	NS
Serum Amylase (D)	ns	NS	NS	NS
Antibodies for Hepatitis A (D)	ns	ns	ns	ns
Serological Evidence of Prior Hepatitis B Infection (D)	–0.004	ns	–0.021	–0.012
Current Hepatitis B (D)	--	NS	--	--
Antibodies for Hepatitis C (D)	ns	ns	ns	ns
Antibodies for Hepatitis D (D)	--	--	--	--
Stool Hemoccult (D)	ns	NS	ns	ns
Prealbumin (C)[a]	ns	NS	NS	NS
Prealbumin (D)	NS	ns	+0.021	NS
Albumin (C)[a]	NS	ns	NS	ns
Albumin (D)	ns	--	--	--
α-1-Acid Glycoprotein (C)	ns	NS	NS	NS
α-1-Acid Glycoprotein (D)	NS	NS	NS	NS
α-1-Antitrypsin (C)	+0.024	NS	+0.011	+0.020

Table 13-78. Summary of Categorized Dioxin Analysis (Model 3) for Gastrointestinal Variables (Ranch Hands vs. Comparisons) (Continued)

	ADJUSTED			
Variable	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
α-1-Antitrypsin (D):				
Low vs. Normal	ns	ns	NS	NS
High vs. Normal	NS	NS	NS	NS
α-2-Macroglobulin (C)	ns	ns	NS	ns
α-2-Macroglobulin (D)	ns*	ns	NS	ns
Apolipoprotein B (C)	ns	ns	NS	ns
Apolipoprotein B (D)	–0.050	ns	ns	ns
C3 Complement (C)[a]	ns	NS	NS	NS
C3 Complement (D)	NS	ns	ns	ns*
C4 Complement (C)[a]	ns	NS	ns	ns
C4 Complement (D)	NS	--	--	--
Haptoglobin (C)	+0.014	NS	NS	+0.036
Haptoglobin (D)	+0.042	NS	NS	NS
Transferrin (C)[a]	NS	NS	+0.050	+0.032
Transferrin (D)	ns	ns	–0.045	–0.039

Note: NS or ns: Not significant (p>0.10).
NS* or ns*: Marginally significant (0.05<p≤0.10).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥1.00 for discrete analysis; difference of means nonnegative for continuous analysis.
–: Relative risk <1.00 for discrete analysis.
--: Analysis not performed because of the sparse number of participants with an abnormality.
[a] Negative difference considered adverse for this variable.

P-value given if p≤0.05.

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

13.4.4 Model 4: 1987 Dioxin Level Analysis

The Model 4 analysis revealed a significant inverse association between jaundice and 1987 dioxin.

Many significant associations between the laboratory examination variables and 1987 dioxin levels were seen in the Model 4 analyses. In both the continuous and discrete forms, the hepatic enzymes ALT, AST, and GGT revealed significant, positive associations with 1987 dioxin. Alkaline phosphatase revealed significant inverse associations with 1987 dioxin in both the continuous and discrete analyses.

For the lipid and carbohydrate indices, the Model 4 continuous and discrete analyses detected significant positive associations with the cholesterol-HDL ratio and triglycerides. A significant inverse relation was seen between 1987 dioxin and HDL cholesterol for both discrete and continuous analyses.

Analysis of creatine phosphokinase in both its continuous and discrete forms revealed a significant positive association with 1987 dioxin. In addition, a significant inverse association between 1987 dioxin and the continuous form of serum amylase was found.

The adjusted results of the protein profile variables yielded several significant findings. A significant inverse association between 1987 dioxin and the continuous form of α-1-acid glycoprotein and a significant positive association between 1987 dioxin and C3 complement in its continuous form were found. The discrete analysis showed more Ranch Hands than Comparisons with a high α-2-macroglobulin level, and more Comparisons than Ranch Hands with low C3 complement and C4 complement levels.

The results of all Model 4 analyses are summarized in Table 13-79.

Table 13-79. Summary of 1987 Dioxin Analysis (Model 4) for Gastrointestinal Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Medical Records		
Uncharacterized Hepatitis (D)	ns	ns
Jaundice (Unspecified) (D)	–<0.001	–<0.001
Chronic Liver Disease and Cirrhosis (Alcohol-related) (D)	NS	NS
Chronic Liver Disease and Cirrhosis (Non-alcohol-related) (D)	NS	NS
Liver Abscess and Sequelae of Chronic Liver Disease (D)	NS	NS
Enlarged Liver (Hepatomegaly) (D)	ns	ns
Other Liver Disorders (D)	NS*	NS*
Physical Examination		
Current Hepatomegaly (D)	NS	NS
Laboratory		
AST (C)	+0.033	+0.002
AST (D)	+0.008	+0.002
ALT (C)	+<0.001	+<0.001
ALT (D)	+0.001	+<0.001
GGT (C)	+0.002	+0.003
GGT (D)	+0.034	+0.012
Alkaline Phosphatase (C)	ns	–0.003
Alkaline Phosphatase (D)	ns	–0.020
Total Bilirubin (C)	ns	NS
Total Bilirubin (D)	ns	ns
Direct Bilirubin (D)	ns	ns
Lactic Dehydrogenase (C)	NS	NS
Lactic Dehydrogenase (D)	NS	NS
Cholesterol (C)	+0.009	NS
Cholesterol (D)	+0.025	NS
HDL Cholesterol (C)[a]	–<0.001	–0.037
HDL Cholesterol (D)	ns	–0.029
Cholesterol-HDL Ratio (C)	+<0.001	+0.006
Cholesterol-HDL Ratio (D)	+<0.001	+0.025
Triglycerides (C)	+<0.001	+<0.001
Triglycerides (D)	+<0.001	+0.001
Creatine Phosphokinase (C)	NS*	+0.011
Creatine Phosphokinase (D)	NS	+0.043
Serum Amylase (C)	–0.035	–0.003
Serum Amylase (D)	ns	ns
Antibodies for Hepatitis A (D)	NS	NS
Serological Evidence of Prior Hepatitis B Infection (D)	+0.023	NS
Current Hepatitis B (D)	NS	NS

Table 13-79. Summary of 1987 Dioxin Analysis (Model 4) for Gastrointestinal Variables (Ranch Hands Only) (Continued)

Variable	Unadjusted	Adjusted
Antibodies for Hepatitis C (D)	ns	ns
Antibodies for Hepatitis D (D)	--	--
Stool Hemoccult (D)	NS	NS
Prealbumin (C)[a]	ns	ns
Prealbumin (D)	NS	NS
Albumin (C)[a]	ns	ns
Albumin (D)	ns	ns
α-1-Acid Glycoprotein (C)	NS	−0.049
α-1-Acid Glycoprotein (D)	NS	ns
α-1-Antitrypsin (C)	NS	ns*
α-1-Antitrypsin (D):		
Low vs. Normal	ns	ns
High vs. Normal	ns	ns
α-2-Macroglobulin (C)	ns	ns
α-2-Macroglobulin (D)	+0.020	+0.014
Apolipoprotein B (C)	+0.002	NS
Apolipoprotein B (D)	+0.017	NS
C3 Complement (C)[a]	+<0.001	+<0.001
C3 Complement (D)	−0.011	−0.004
C4 Complement (C)[a]	NS*	NS
C4 Complement (D)	−0.033	−0.024
Haptoglobin (C)	NS	ns
Haptoglobin (D)	NS	ns
Transferrin (C)[a]	NS*	NS
Transferrin (D)	NS	NS

Note: NS or ns: Not significant (p>0.10).
NS* or ns*: Marginally significant (0.05<p≤0.10).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥1.00 for discrete analysis; slope nonnegative for continuous analysis.
−: Relative risk <1.00 for discrete analysis; slope negative for continuous analysis.
--: Analysis not performed because of the sparse number of Ranch Hands with an abnormality.
[a] Negative slope considered adverse for this variable.

P-value given if p≤0.05.

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

13.5 CONCLUSION

The gastrointestinal assessment was based on eight disorders as determined from a review and verification of each participant's medical records, a physical examination determination of hepatomegaly, and 29 laboratory measurements or indices. The laboratory parameters included measurements of hepatic enzyme activity, hepatobiliary function, lipid and carbohydrate indices, and a protein profile. In addition, the presence of hepatitis and fecal occult blood was investigated.

Analyses of Ranch Hands versus Comparisons showed higher mean levels of alkaline phosphatase, α-1-antitrypsin, and haptoglobin in Ranch Hands than in Comparisons. In addition, significantly more Ranch Hands than Comparisons had high haptoglobin levels. A review of medical records showed a positive association between initial dioxin and other liver disorders. Twelve percent of the participants with the other liver disorders condition had nonspecific laboratory test elevations. A significant association between initial dioxin and high levels of AST also was revealed.

Analyses of categorized dioxin revealed a significantly higher percentage of other liver disorders among Ranch Hands in the high dioxin category than among Comparisons. Higher mean levels of GGT, triglycerides, and α-1-antitrypsin were observed in Ranch Hands in the high dioxin category than in Comparisons. Ranch Hands in the high dioxin category had a greater prevalence of abnormal AST, triglyceride, and prealbumin levels than did Comparisons.

Many significant associations between the laboratory examination variables and 1987 dioxin levels were observed. In both the continuous and discrete forms, the hepatic enzymes ALT, AST, and GGT revealed significant, positive associations with 1987 dioxin. In addition, significant positive associations between 1987 dioxin and the cholesterol-HDL ratio, triglycerides, and creatine phosphokinase were present.

In summary, the analysis of the 1997 follow-up data reflected patterns that have been observed and documented in prior examinations. A composite category of disease named "other liver disorders" exhibited a dose-response relation with dioxin. Isolated group differences exist, but 1987 dioxin levels are strongly related to hepatic enzymes such as AST, ALT, and GGT, and to lipid-related health indices such as cholesterol, HDL, and triglycerides. These results are consistent with a dose-response effect and may be related to unknown subclinical effects of dioxin. Although hepatic enzymes showed an association with dioxin, there was no evidence of an increase in overt liver disease. The relation between other liver disorders and herbicide exposure and dioxin levels will be described in greater detail in a separate report.

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14 CARDIOVASCULAR ASSESSMENT

14.1 INTRODUCTION

14.1.1 Background

Animal research into the cardiotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) has focused on acute biochemical and functional abnormalities associated with high-level exposure. In one study (1), rats were found to have reductions in pulse and blood pressure 6 days after administration of 40 μg/kg of dioxin by gavage and were less responsive to the chronotropic effect of isoproterenol, a beta-agonist. The authors of the study, noting a 66-percent reduction in serum thyroxine, postulated a down regulation of beta-receptors associated with the hypothyroid state rather than a direct cardiotoxic effect. Their findings were consistent with other studies that documented changes in myocardial beta-receptors with reduced serum indices of thyroid function and decreased beta-adrenergic responsiveness to isoproterenol in the ventricular papillary muscle of guinea pigs (2). Experiments into the effects of dioxin on myocardial contractility in rat (3) and guinea pig (4) atrial muscle have yielded mixed results; the primary cardiotoxic effects remain uncertain.

The biochemical effects of dioxin on cardiac muscle have been the subject of several reports. An increase in lipid peroxidation and a decrease in superoxide dismutase activity were noted in the hearts of female rats after dioxin administration (1). Dose-dependent decreases in adipose tissue lipoprotein lipase activity and hepatic low-density lipoprotein binding occurred in rabbits (5) and other laboratory animals (6) in association with elevated serum triglycerides. Electron microscopic studies have documented pre-atherosclerotic lesions in the aortic arch in association with these biochemical abnormalities (5) and dioxin exposure has been associated with intravascular thrombosis in rats (7). Two recent studies provide evidence that the developing vascular endothelium of fish embryos may be a target organ for dioxin toxicity (8, 9).

Numerous studies have focused on the effects of dioxin toxicity on lipid metabolism in experimental animals and may be relevant to herbicide exposure as a risk factor for the development of heart disease in man. Dioxin-induced hyperlipidemia has been documented in rats (10, 11), guinea pigs (12), and rabbits (5).

Numerous epidemiological studies have investigated cardiovascular mortality and morbidity in populations exposed to dioxin by occupation and consequent to industrial accidents (13–22). Other reports have examined similar endpoints in veterans who served in the Vietnam War (23–35). Some occupational (13, 20) and veterans' studies (23, 25, 26, 28–31) cited have shown no increase in cardiovascular mortality associated with exposure to dioxin, and several have documented a significant reduction in risk (23, 26, 27). However, in the 1994 Air Force Health Study (AFHS) mortality update (36), the Ranch Hand nonflying enlisted personnel were found to be at higher risk for death associated with circulatory disease than the Comparison nonflying enlisted personnel. Most occupational studies have found no increased risk for the development of cardiovascular disease related to dioxin exposure (13–16, 20). In two reports of the 1976 Seveso, Italy, industrial accident, dioxin exposure was associated with statistically significant increases in mortality because of coronary, cerebrovascular, and hypertensive vascular disease (18, 19).

The latest morbidity follow-up study of BASF Corporation employees highly exposed to dioxin during a chemical reactor incident in 1953 has been published (21). Almost half of the study group had extrapolated serum dioxin levels of more than 1,000 parts per trillion (ppt). Across all exposure categories, there was no significant increase in the incidence of ischemic heart disease.

A more recently published retrospective cohort study examined cardiovascular mortality in 1,189 German chemical workers who had significant dioxin exposure in the 1950s (37). In this study, exposure was verified and subjects stratified into deciles based on serum and adipose tissue dioxin levels. There was a slight reduction in mortality risk at the two lowest levels of exposure, but a clear pattern of increasing risk for all-cause cardiovascular mortality and, particularly, for that associated with ischemic heart disease. The dose-response trend for both causes of mortality was significant ($p \leq 0.01$).

The well-established roles of diabetes mellitus and lipid disorders as risk factors in the development of cardiovascular disease have generated considerable interest in the potential intermediary role these metabolic indices might have on cardiovascular outcomes associated with dioxin exposure. Data and results from this (35, 38) and other epidemiological studies (22, 37, 39–44) are considered in the Gastrointestinal Assessment chapter (Chapter 13) and the Endocrine Assessment chapter (Chapter 16).

Previous AFHS examinations have shown mixed results with respect to cardiovascular endpoints. In the baseline and 1987 follow-up examinations, manual examination of the pulses revealed an increased prevalence of pulse deficits in the Ranch Hand cohort relative to Comparisons (45, 46), results noted as well in studies of residents exposed to dioxin in Times Beach, Missouri (47, 48). In the 1985 AFHS follow-up examination, which incorporated Doppler peripheral vascular studies into the protocol, no significant group differences were found (49). When the 1987 examination data were analyzed relative to serum dioxin levels, Ranch Hand participants in one high exposure category had higher percentages of peripheral pulse abnormalities by manual examination than did Comparisons (34). In addition, Ranch Hands with the highest current dioxin levels were at greater risk for the development of systemic arterial hypertension than were Comparisons. In contrast, there was a significant reduction in risk for the development of heart disease reported historically or by a verified medical records review.

In the 1992 follow-up examination, Ranch Hands were more likely than Comparisons to have elevated systolic blood pressures, and through 1990, there was an increase in cardiovascular disease mortality in the nonflying enlisted personnel. However, surviving Ranch Hands overall were found to be less at risk for the development of heart disease over time, and a significant inverse dose-response effect was noted with respect to the current body burden of dioxin (35).

14.1.2 Summary of Previous Analyses of the Air Force Health Study

14.1.2.1 1982 Baseline Study Summary Results

The 1982 baseline examination found no statistically significant differences between the Ranch Hand and Comparison groups in systolic or diastolic blood pressure, the frequency of abnormal electrocardiographs (ECGs), heart sound abnormalities, abnormal funduscopic findings, or carotid bruits. A statistically significant difference emerged in the frequency of abnormal peripheral pulses: 12.8 percent of the non-Black Ranch Hands exhibited absent or diminished peripheral pulses, compared to 9.4 percent of the non-Black Original Comparisons ($p=0.05$). No statistically significant differences were found between the two groups in the occurrence of reported or verified heart disease or heart attacks.

Greater than 80 percent of the cardiac conditions reported on the study questionnaire were verified by a detailed review of medical records. There was also a strong correlation between the past medical history of cardiac disease and the baseline examination cardiovascular findings, although the differences in peripheral pulse abnormalities occurred primarily in older individuals without a history of cardiovascular disease. Finally, the well-known risk factors of age, smoking, and cholesterol were found to be correlated with each other and with several of the cardiovascular response variables.

14.1.2.2 1985 Follow-up Study Summary Results

The analysis of cardiovascular disease history did not reveal significant group differences in reported or verified hypertension, reported heart disease, or reported or verified heart attacks. There were no group differences in verified heart disease. The verified cardiovascular history and the central and peripheral cardiovascular abnormalities detected at the physical examination were correlated, supporting accuracy and validity of the cardiovascular measurements.

In the analyses of peripheral vascular function, no significant overall group differences were observed for abnormalities involving radial, femoral, popliteal, posterior tibial, dorsalis pedis, or three anatomic aggregates of these pulses (leg pulses, peripheral pulses, and all pulses), either by manual palpation or Doppler techniques. This overall finding was in distinct contrast to the 1982 baseline examination, which, by the manual palpation method, showed significant peripheral pulse deficits in Ranch Hands. This reversal in pulse findings over the two examinations may be attributed to the rigid 4-hour tobacco abstinence applied prior to Doppler testing, although other factors may have been involved.

14.1.2.3 1987 Follow-up Study Summary Results

The assessment of the central cardiac function also found the groups to be similar, although significantly fewer Ranch Hands than Comparisons had bradycardia and more Ranch Hands than Comparisons had arrhythmias (marginally significant).

For the peripheral vascular function, Ranch Hands had a higher or marginally higher mean or percent abnormal for diastolic blood pressure (continuous form), carotid bruits, femoral pulses, and dorsalis pedis pulses than did Comparisons. No difference between the two groups was detected in the discrete analysis of diastolic blood pressure. The percentage of radial pulse abnormalities was marginally higher in Comparisons than in Ranch Hands. On the three pulse indices (leg, peripheral, and all pulses), Ranch Hands had marginally or significantly higher percentages of abnormalities than did Comparisons.

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

The cardiovascular evaluation found a marginally significant association between initial dioxin and a decrease in the reported history of heart disease, and a significant negative association with verified history of heart disease. In addition, the analyses of categorized current dioxin also indicated a decrease in verified history of heart disease for Ranch Hands with the highest current dioxin levels relative to Comparisons with background levels. These Ranch Hands also had more essential hypertension by history (after removing the variables body fat and cholesterol from the model).

The analyses of the peripheral vascular function variables displayed significantly higher mean levels of diastolic blood pressure for Ranch Hands in the low and high categories than Comparisons (without adjustment for body fat). Similar to the analysis of systolic blood pressure, the discretized analysis of diastolic blood pressure did not display a significant association with dioxin within the low and high current dioxin categories. Ranch Hands generally exhibited a significant or marginally significant higher risk of absent femoral, dorsalis pedis, and posterior tibial pulses relative to Comparisons. These observations could represent a subclinical effect and emphasize the importance of continued follow-up and evaluation.

14.1.2.5 1992 Follow-up Study Summary Results

The cardiovascular evaluation found a marginally significant group difference for verified heart disease, excluding essential hypertension for enlisted flyers with Ranch Hands having a greater history of heart disease than Comparisons. Similar to the 1987 study, verified heart disease decreased significantly for increasing levels of current dioxin. Ranch Hands also displayed an increased history of essential hypertension for increasing levels of current dioxin.

A few other central cardiac function endpoints, including non-specific ST- and T-wave changes, right bundle branch block, and prior ECG evidence of myocardial infarction, displayed significant positive associations with current dioxin; none of these endpoints also displayed any group difference between Ranch Hands and Comparisons. These findings, in conjunction with the increase in the number of deaths caused by diseases of the circulatory system for Ranch Hand nonflying enlisted personnel based on the 1994 AFHS mortality update (34), showed potential associations with dioxin requiring further observation.

The analyses of the peripheral vascular function variables displayed significant group differences for the enlisted groundcrew stratum for a few of the pulse endpoints and significant differences between Ranch Hands in the high dioxin category and Comparisons. None of these associations was reinforced by a significant association with initial or current dioxin. Longitudinal analyses of the pulse endpoints also indicated that Ranch Hands in the enlisted groundcrew stratum and in the high initial dioxin category had a greater prevalence of pulse deficits since the 1985 follow-up examination than Comparisons. Again, these associations were not reinforced by a significant dose-response effect with initial dioxin.

In general, after reviewing the results of the cardiovascular assessment as a whole, the development of cardiovascular disease did not appear to be associated positively with dioxin. Dioxin associations with selected endpoints, as discussed above, together with mortality results, pointed to the need for further evaluation.

14.1.3 Parameters for the 1997 Cardiovascular Assessment

14.1.3.1 Dependent Variables

The analysis of the cardiovascular assessment was based on data collected from the 1997 questionnaire and physical examination and subsequent medical records verification. No laboratory examination data were analyzed as cardiovascular dependent variables, although data from the laboratory examination were used as covariates.

14.1.3.1.1 Medical Records Data

During the baseline, 1985, 1987, and 1992 AFHS examination health interviews, each participant was asked whether he had a heart condition. Medical records were sought to verify all reported conditions and to determine the time of occurrence of major cardiac events. In addition, the self-reported review-of-systems recorded the overall history of heart trouble and other serious illnesses. Data collected in a similar fashion at the 1997 follow-up was verified and combined with data from the four previous examinations to create a lifetime history for four conditions: essential hypertension, heart disease (excluding essential hypertension), myocardial infarction, and stroke or transient ischemic attack. Each of these conditions was classified as "yes" or "no" and analyzed.

International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to construct the four conditions described above. The following ICD-9-CM codes were used: essential hypertension (ICD-9-CM codes 401.0-401.9), heart disease (excluding essential hypertension)

(ICD-9-CM codes 391.0-391.9, 392.0, 393.0-398.99, 402.0-402.91, 404.0-404.9, 410.0-417.9, and 420.0-429.9), myocardial infarction (ICD-9-CM codes 410.0-410.9, and 412), and stroke or transient ischemic attack (ICD-9-CM codes 435.0-436).

Participants with a verified pre-SEA heart condition were excluded from all analyses. A pre-SEA heart condition included pre-SEA myocardial infarction, but did not include pre-SEA essential hypertension. Participants with a verified pre-SEA history of essential hypertension also were excluded from the analysis of verified history of essential hypertension.

14.1.3.1.2 Physical Examination Data and Self-reported Questionnaire Data

Cardiovascular data analyzed from the 1997 physical examination were divided into two main categories: central cardiac function and peripheral vascular function.

14.1.3.1.2.1 Central Cardiac Function

The assessment of the central cardiac function at the cardiovascular examination was made by measurements of systolic blood pressure, diastolic blood pressure, heart sounds (by auscultation), and an ECG. Systolic and diastolic blood pressure were determined by a Critikon Dinamap 1846SXP® automated electronic monitor with the nondominant arm placed at heart level; the lowest diastolic pressure and the corresponding systolic pressure were recorded. Detection of abnormal heart sounds was conducted by standard auscultation with the participant placed in sitting, supine, and left lateral supine positions. Fourth heart sounds were assessed; murmurs were graded in intensity and location and were judged by the examiners to be functional (normal) or organic (abnormal) in nature. The standard 12-lead ECG was performed, and an additional strip in limb lead II was produced if any arrhythmia was found. Participants were asked to abstain from tobacco for at least 4 hours prior to the ECG because of the arterial constrictive effect of nicotine. The following items were considered to be abnormal: right bundle branch block, left bundle branch block, nonspecific ST- and T-wave changes, bradycardia (a resting pulse rate less than 50 beats per minute), tachycardia (a resting pulse rate greater than 100 beats per minute), arrhythmia (any irregularity of heart rhythm including premature beats but excluding normal sinus rhythm), evidence of a prior myocardial infarction, and other diagnoses (e.g., ventricular aneurysm, Wolff-Parkinson-White syndrome). Some arrhythmias (e.g., atrial flutter, atrial fibrillation, and junctional rhythm) required more evaluation and surveillance than others, but all were grouped together for evaluation in this study.

Variables analyzed in the evaluation of the central cardiac function included systolic blood pressure, diastolic blood pressure, heart sounds, an overall ECG assessment, and eight conditions associated with the ECG. These eight conditions were right bundle branch block, left bundle branch block, nonspecific ST- and T-wave changes, bradycardia, tachycardia, arrhythmia, evidence of a prior myocardial infarction, and other diagnoses. Both systolic and diastolic blood pressure were analyzed as a continuous variable and also as a discrete variable. Systolic blood pressure was classified as "normal" (≤140 mm Hg) and "high" (>140 mm Hg), and diastolic blood pressure was classified as "normal" (≤90 mm Hg) and "high" (>90 mm Hg). Participants with a verified pre-SEA heart condition were excluded from all analyses of the central cardiac function variables.

14.1.3.1.2.2 Peripheral Vascular Function

The peripheral vascular function was assessed during the cardiovascular examination by funduscopic examination of small vessels; presence or absence of carotid bruits; determination of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses by Doppler techniques; and a measure of intermittent claudication and vascular insufficiency.

The funduscopic examination was conducted with undilated pupils in a standard manner, with emphasis placed upon the detection of increased light reflex, arteriovenous nicking (a sign of chronic blood pressure elevation), hemorrhages, exudates, papilledema, and arteriolar spasm. The presence or absence of carotid bruits was assessed by auscultation over both carotid arteries.

The Doppler procedure for examining pulses is a progressive array of measurements designed to determine whether a pulse abnormality exists, where the obstruction is most likely located, and whether it has functional implications. The determination of a pulse abnormality was based upon an analysis of recorded Doppler waveform morphology. Pulsatility, systolic forward flow, diastolic reverse flow, and diastolic oscillations were examined.

The funduscopic examination, carotid bruits, and the five pulses also were dichotomized as "abnormal" or "normal" (or "presence" or "absence") and analyzed. Pulses were considered abnormal if no arterial flow or a monophasic arterial flow was present on either side. In addition, two pulse indices were constructed from the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulse measurements as follows:

- Leg pulses: femoral, popliteal, dorsalis pedis, and posterior tibial pulses
- Peripheral pulses: radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses.

Each of these indices was considered "normal" if all components were normal and "abnormal" if one or more pulses were abnormal.

In the 1997 questionnaire, each participant was asked the following questions:

- Do you get a pain in either or both of your legs while walking?
- Does this pain ever begin when you are standing still or sitting?
- Do you get this pain in either or both of your calf muscles?

The self-reported answers were used to detect intermittent claudication and vascular insufficiency (yes, no), which indicate an insufficient oxygen supply to the leg muscles. A participant was judged to have intermittent claudication and vascular insufficiency if he answered "yes" to the first and third questions and "no" to the second question. Participants with a verified pre-SEA heart condition were excluded from all analyses of the peripheral vascular function variables.

14.1.3.2 Covariates

A number of covariates were examined for inclusion in the adjusted analysis of the cardiovascular assessment. Many of these covariates are considered to be classical risk factors for chronic heart disease. Covariates examined included age, race, military occupation, lifetime alcohol history, current alcohol use, lifetime cigarette smoking history, current level of cigarette smoking, cholesterol, high-density lipoprotein (HDL), cholesterol-HDL ratio, body fat, personality type, family history of heart disease, family history of heart disease before the age of 45, diabetic class, and current use of blood pressure medication (for the blood pressure variables).

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

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

Cholesterol, HDL, and the cholesterol-HDL ratio were based on 1997 laboratory measurements. Body fat was calculated from a metric body mass index (50); the formula is

$$Body\ Fat\,(in\ percent) = \frac{Weight\,(kg)}{[Height\,(m)\,]^2} \bullet\ 1.264 - 13.305.$$

Personality type was determined from the Jenkins Activity Survey administered during the 1997 follow-up examination and was derived from a discriminant-function equation based on questions that best discriminate men judged to be type A from those judged to be type B (51). Positive scores reflected the type A direction and negative scores reflected the type B direction. Personality type was dichotomized as type A or type B.

Family history of heart disease was defined as "yes" if the participant's mother, father, sister(s), or brother(s) had heart trouble or heart disease and "no" otherwise. Family history of heart disease before the age of 45 was defined as "yes" if the participant's mother, father, sister(s), or brother(s) had heart trouble or heart disease before the age of 45 and "no" otherwise. Blood pressure medication (yes, no) was used as a covariate for the adjusted analysis of the systolic and diastolic blood pressure variables only.

Diabetic class was used as a covariate in the analysis of the 1997 follow-up. Diabetes is a known risk factor for cardiovascular disease. In the 1997 questionnaire, a general screening question on diabetes was posed. Each participant was asked during the in-person health interview the following question: "Since the date of the last interview, has a doctor told you for the first time that you had diabetes?" All affirmative responses were verified by a medical records review and added to previously reported and verified information on diabetes from the 1982 baseline and the 1985, 1987, and 1992 follow-up examinations for each participant. Participants with a verified history of diabetes were combined with those participants with a 2-hour postprandial glucose level of 200 mg/dl or greater at the 1997 physical examination and classified as "diabetic" for the diabetic class covariate. Those participants without a verified history of diabetes and with a 2-hour postprandial glucose level of less than 200 mg/dl at the 1997 physical examination were classified as either "impaired" (140 mg/dl $\leq$ 2-hour postprandial glucose $<$ 200 mg/dl) or "normal" (2-hour postprandial glucose $<$ 140 mg/dl).

The current use of blood pressure medication was used as a covariate for the adjusted analysis of systolic and diastolic blood pressures. This information was reported by the participant on a self-reported form that listed physicians and medications, and through a question in the in-person interview.

The following dependent variables—essential hypertension, heart disease excluding essential hypertension, myocardial infarction, and stroke or transient ischemic attack—capture a history of a cardiovascular condition rather than the current state of a participant's life at the time of the physical examination. Consequently, to reflect the historical nature of these dependent variables, lifetime alcohol history and lifetime cigarette smoking history were used as covariates, but current alcohol use and current cigarette smoking were not. Lifetime alcohol history and lifetime cigarette smoking history reflect the cumulative lifetime effects of alcohol use and tobacco, respectively, whereas current alcohol use and current cigarette smoking emphasize the short period of time near the date of the physical examination.

14.1.4 Statistical Methods

Table 14-1 summarizes the statistical analysis performed for the cardiovascular assessment. The first part of this table describes the dependent variables and identifies the covariates and the statistical methods. The second part of this table further describes the covariates. A covariate was used in its continuous form whenever possible for all adjusted analyses. If a 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 14-1.

Table 14-2 provides a summary of the number of participants with missing dependent variable or covariate data. In addition, the number of participants excluded from analysis is given.

Table 14-1. Statistical Analysis for the Cardiovascular Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Covariates[a]	Exclusions[b]	Statistical Analysis and Methods
Essential Hypertension	MR-V	D	Yes No	(1)	(a)	U:LR A:LR
Heart Disease (Excluding Essential Hypertension)	MR-V	D	Yes No	(1)	(b)	U:LR A:LR
Myocardial Infarction	MR-V	D	Yes No	(1)	(b)	U:LR A:LR
Stroke or Transient Ischemic Attack	MR-V	D	Yes No	(1)	(b)	U:LR,CS A:LR
Systolic Blood Pressure (mm Hg)	PE	D/C	High: >140 Normal: ≤140	(2)	(b)	U:LR,GLM A:LR,GLM L:LR,GLM
Diastolic Blood Pressure (mm Hg)	PE	D/C	High: >90 Normal: ≤90	(2)	(b)	U:LR,GLM A:LR,GLM
Heart Sounds	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR
Overall Electrocardiograph (ECG)	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR
ECG: Right Bundle Branch Block	PE	D	Yes No	(3)	(b)	U:LR A:LR
ECG: Left Bundle Branch Block	PE	D	Yes No	(3)	(b)	U:LR,CS A:LR
ECG: Non-specific ST-and T-Wave Changes	PE	D	Yes No	(3)	(b)	U:LR A:LR
ECG: Bradycardia	PE	D	Yes No	(3)	(b)	U:LR A:LR
ECG: Tachycardia	PE	D	Yes No	(3)	(b)	U:LR,CS A:LR

Table 14-1. Statistical Analysis for the Cardiovascular Assessment (Continued)

Variable (Units)	Data Source	Data Form	Cutpoints	Covariates[a]	Exclusions[b]	Statistical Analysis and Methods
ECG: Arrhythmia	PE	D	Yes No	(3)	(b)	U:LR A:LR
ECG: Evidence of Prior Myocardial Infarction	PE	D	Yes No	(3)	(b)	U:LR A:LR
ECG: Other Diagnoses	PE	D	Yes No	(3)	(b)	U:LR,CS A:LR
Funduscopic Examination	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR
Carotid Bruits	PE	D	Present Absent	(3)	(b)	U:LR A:LR
Radial Pulses	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR
Femoral Pulses	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR L:LR
Popliteal Pulses	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR L:LR
Dorsalis Pedis Pulses	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR L:LR
Posterior Tibial Pulses	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR L:LR
Leg Pulses	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR L:LR
Peripheral Pulses	PE	D	Abnormal Normal	(3)	(b)	U:LR A:LR L:LR
Intermittent Claudication and Vascular Insufficiency (ICVI) Index	Q-SR	D	Abnormal Normal	(3)	(b)	U:LR A:LR

[a]Covariates:
(1): age, race, military occupation, lifetime cigarette smoking history, lifetime alcohol history, cholesterol, HDL, cholesterol-HDL ratio, diabetic class, body fat, personality type, family history of heart disease, family history of heart disease before age 45.
(2): age, race, military occupation, lifetime cigarette smoking history, current cigarette smoking, lifetime alcohol history, current alcohol use, cholesterol, HDL, cholesterol-HDL ratio, diabetic class, body fat, personality type, family history of heart disease, family history of heart disease before age 45, taking blood pressure medication.
(3): age, race, military occupation, lifetime cigarette smoking history, current cigarette smoking, lifetime alcohol history, current alcohol use, cholesterol, HDL, cholesterol-HDL ratio, diabetic class, body fat, personality type, family history of heart disease, family history of heart disease before age 45.

[b]Exclusions:
(a): participants with a pre-SEA heart condition, participants with pre-SEA essential hypertension.
(b): participants with a pre-SEA heart condition.

Table 14-1. Statistical Analysis for the Cardiovascular Assessment (Continued)

Covariates

Variable (Units)	Data Source	Data Form	Cutpoints
Age (years)	MIL	D/C	Born ≥1942 Born <1942
Race	MIL	D	Black Non-Black
Occupation	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Lifetime Alcohol History (drink-years)	Q-SR	D/C	0 >0–40 >40
Current Alcohol Use (drinks/day)	Q-SR	D/C	0–1 >1–4 >4
Lifetime Cigarette Smoking History (pack-years)	Q-SR	D/C	0 >0–10 >10
Current Cigarette Smoking (cigarettes/day)	Q-SR	D/C	0-Never 0-Former >0–20 >20
Cholesterol (mg/dl)	LAB	D/C	≤200 >200–239 >239
High Density Lipoprotein (mg/dl)	LAB	D/C	0–35 >35
Cholesterol-HDL Ratio	LAB	D/C	0–5 >5
Body Fat (percent)	PE	D/C	Obese: >25% Lean or Normal: ≤25%
Personality Type	PE	D	A direction B direction
Family History of Heart Disease	Q-SR	D	Yes No
Family History of Heart Disease Before Age 45	Q-SR	D	Yes No
Diabetic Class	LAB/MR-V	D	• Diabetic: past history or ≥200 mg/dl 2-hr. postprandial glucose • Impaired: 140–<200 mg/dl 2-hr. postprandial glucose • Normal: <140 mg/dl 2-hr. postprandial glucose
Taking Blood Pressure Medication	Q-SR/MR-V	D	Yes No

Table 14-1. Statistical Analysis for the Cardiovascular Assessment (Continued)

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)

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 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

Table 14-2. Number of Participants Excluded or with Missing Data for the Cardiovascular Assessment

		Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
Variable	Variable Use	Ranch Hand	Comparison	Initial	1987	Ranch Hand	Comparison
Funduscopic Examination	DEP	1	1	0	1	1	1
Femoral Pulses	DEP	0	1	0	0	0	1
Popliteal Pulses	DEP	0	2	0	0	0	2
Dorsalis Pedis Pulses	DEP	0	2	0	0	0	2
Posterior Tibial Pulses	DEP	0	4	0	0	0	4
Leg Pulses	DEP	0	4	0	0	0	4
Peripheral Pulses	DEP	0	4	0	0	0	4
Intermittent Claudication and Insufficiency Index	DEP	1	0	0	1	1	0
Lifetime Alcohol History	COV	6	2	3	6	6	1
Current Alcohol Use	COV	1	0	0	1	1	0
Lifetime Cigarette Smoking History	COV	2	1	1	2	2	1
Current Cigarette Smoking	COV	1	0	0	1	1	0
HDL Cholesterol	COV	1	1	1	1	1	1
Cholesterol-HDL Ratio	COV	1	1	1	1	1	1
Personality Type	COV	3	0	1	3	3	0
Family History of Heart Disease	COV	10	6	5	10	10	6
Family History of Heart Disease Before Age 45	COV	22	22	11	22	22	21
Diabetic Class	EXC	9	18	5	7	7	17

Table 14-2. Number of Participants Excluded or with Missing Data for the Cardiovascular Assessment (Continued)

		Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
Variable	Variable Use	Ranch Hand	Comparison	Initial	1987	Ranch Hand	Comparison
Pre-SEA Heart Condition	EXC	11	19	6	11	11	18
Pre-SEA Essential Hypertension	EXC	11	14	7	11	11	14

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.

14.1.4.1 Longitudinal Analysis

The cardiovascular longitudinal analysis was based on the association of exposure with changes in systolic blood pressure between the 1982 and 1997 examinations and six pulse measurements between the 1985 and 1997 examinations. The longitudinal analysis for systolic blood pressure was based on this variable in both the continuous and discrete forms. The six pulse measurements included femoral pulses, popliteal pulses, dorsalis pedis pulses, posterior tibial pulses, leg pulses, and peripheral pulses. The 1985 and 1997 measurements were used for the pulse assessments because the Doppler assessment of pulses was conducted at these two examinations and was not conducted at the 1982 baseline examination.

14.2 RESULTS

14.2.1 Dependent Variable-Covariate Associations

The associations between the dependent variables examined in the cardiovascular assessment and the covariates used in the adjusted analysis were investigated; the results are presented in Appendix F, Table F-6. These associations are pairwise between the dependent variable and the covariate and are not adjusted for any other covariates. Participants with a pre-SEA heart condition were excluded from all analyses. In addition, participants with pre-SEA essential hypertension were excluded from the analysis of essential hypertension.

Tests of covariate association showed age (p=0.001), lifetime alcohol history (p=0.001), cholesterol-HDL ratio (p=0.005), body fat (p=0.001), personality type (p=0.039), family history of heart disease (p=0.001), family history of heart disease before age 45 (p=0.003), and diabetic class (p=0.001) to be significantly associated with essential hypertension. Older participants had more essential hypertension than did younger participants (48.0% versus 32.9%). Essential hypertension was highest for the heaviest drinkers (in terms of drink-years) (48.2%), followed by participants who did not drink (39.0%), then moderate drinkers (38.5%). Essential hypertension increased with the cholesterol-HDL ratio and body fat. Participants with personality type B had a higher percentage of essential hypertension than did type A participants (43.0% versus 38.4%). Essential hypertension occurred more often for participants who had a family history of heart disease and for participants who had a family history of heart disease before age 45. Essential hypertension was greatest for diabetics (59.4%), followed by participants in the impaired diabetic class (52.4%), then participants classified as normal (34.6%).

Heart disease (excluding essential hypertension) was significantly associated with age (p=0.001), occupation (p=0.001), cholesterol (p=0.001), family history of heart disease (p=0.001), family history of heart disease before age 45 (p=0.018), and diabetic class (p=0.009). Heart disease increased with age and decreased with cholesterol level. Officers had the highest percentage of heart disease (68.7%), followed by enlisted flyers (66.6%), then enlisted groundcrew (56.7%). Participants with a family history of heart disease had more heart disease (66.6% versus 57.4%). Likewise, participants with a family history of heart disease before age 45 had more heart disease (69.9% versus 62.0%). Diabetic participants had the most heart disease (69.5%), followed by participants in the impaired diabetic class (64.1%), then participants classified as normal (60.8%).

The percentage of participants with a history of a myocardial infarction increased significantly with age (p=0.001) and lifetime cigarette smoking history (p=0.001), while decreasing significantly with cholesterol (p=0.001) and HDL cholesterol (p=0.012). The association with diabetic class was also significant (p=0.001). Participants in the normal diabetic class had the lowest percentage of participants with a myocardial infarction (6.8%), followed by participants in the impaired diabetic class (9.9%), then diabetics (14.2%).

Systolic blood pressure in its continuous form increased with age (p<0.001), lifetime alcohol history (p<0.001), lifetime cigarette smoking history (p=0.045), cholesterol (p=0.012), the cholesterol-HDL ratio (p=0.005), and body fat (p<0.001). Systolic blood pressure decreased significantly with current cigarette smoking (p=0.004). Tests of covariate associations also showed significant relations with occupation (p=0.005), diabetic class (p<0.001), and blood pressure medication (p<0.001). Enlisted flyers had the highest mean systolic blood pressure levels (127.1 mm Hg), followed by officers (126.1 mm Hg), then enlisted groundcrew (123.9 mm Hg). Participants in the normal diabetic class had the lowest mean systolic blood pressure levels (123.0 mm Hg), followed by participants in the impaired diabetic class (129.3 mm Hg), then diabetic participants (131.8 mm Hg). Participants taking blood pressure medication had a higher mean systolic blood pressure level (128.6 mm Hg) than those not taking blood pressure medication (123.9 mm Hg).

Systolic blood pressure in its dichotomous form increased with age (p=0.001), cholesterol (p=0.025), the cholesterol-HDL ratio (p=0.028), and body fat (p=0.001). Significant associations also were seen between systolic blood pressure and occupation (p=0.029), family history of heart disease (p=0.008), diabetic class (p=0.001), and blood pressure medication (p=0.001). Enlisted flyers had the greatest percentage of high systolic blood pressure values (23.6%), followed by officers (23.2%), then enlisted groundcrew (18.6%). Participants with a family history of heart disease had a greater prevalence of high systolic blood pressure values than did participants with no history of heart disease (23.3% versus 18.3%). Diabetic participants had the largest percentage of high systolic blood pressure values (31.9%), followed by participants in the impaired diabetic class (28.6%), then participants classified as normal (17.1%). Participants taking blood pressure medication had a greater prevalence of high systolic blood pressure values than participants not taking blood pressure medication (27.6% versus 18.5%).

Diastolic blood pressure in its continuous form decreased with age (p=0.009), lifetime cigarette smoking history (p=0.003), and current cigarette smoking (p=0.001). Diastolic blood pressure increased with cholesterol (p<0.001), the cholesterol-HDL ratio (p=0.004), and body fat (p<0.001). Race and diabetic class were also significantly associated with diastolic blood pressure (p=0.010 and p=0.030, respectively). Black participants had a higher mean diastolic blood pressure than non-Black participants (76.69 mm Hg versus 74.46 mm Hg). Participants in the impaired diabetic class had the highest mean diastolic blood pressure (75.94 mm Hg), followed by diabetic participants (74.41 mm Hg), then participants classified as normal (74.32 mm Hg).

Tests of covariate association for diastolic blood pressure in its discrete form showed significant relations with lifetime cigarette smoking history (p=0.003) and blood pressure medication (p=0.004). Moderate lifetime cigarette smokers (in terms of pack-years) had the greatest percentage of high diastolic blood pressure values (7.8%), followed by participants who never smoked and participants who were the heaviest smokers (4.1% each). Participants taking blood pressure medication had a greater prevalence of high diastolic blood pressure values than did participants not taking blood pressure medication (7.3% versus 4.1%).

The percentage of participants with abnormal heart sounds increased with age (p=0.001). Current cigarette smoking was also significantly associated with heart sounds (p=0.030). Former smokers had the highest prevalence of abnormal heart sounds (5.7%), followed by participants who smoked up to 20 cigarettes per day (3.4%), participants who smoked more than 20 cigarettes per day (2.9%), and participants who never smoked (2.9%).

The prevalence of abnormal overall ECG results increased with age (p=0.001) and body fat (p=0.008), while decreasing with cholesterol (p=0.041). Also significant were occupation (p=0.001), lifetime cigarette smoking history (p=0.002), current cigarette smoking (p=0.028), personality type (p=0.011), family history of heart disease (p=0.001), and diabetic class (p=0.001). Enlisted flyers had the highest percentage of abnormal overall ECG results (36.4%), followed by officers (34.6%), then enlisted groundcrew (26.3%). Heavy lifetime cigarette smokers (in terms of pack-years) had the highest percentage of abnormal overall ECG results (35.0%), followed by participants who never smoked (28.3%), then moderate lifetime cigarette smokers (27.6%). Participants who currently smoked up to 20 cigarettes per day had the highest percentage of abnormal overall ECG results (35.0%), followed by former smokers (32.8%), participants who never smoked (28.3%), and participants who smoked more than 20 cigarettes per day (23.5%). Participants with type B personalities had a higher percentage of abnormal overall ECG results (33.2%) than did participants with type A personalities (27.8%). Participants with a family history of heart disease had a higher prevalence of abnormal overall ECG results than did participants with no family history of heart disease (35.3% versus 24.6%). Diabetic participants had the highest percentage of abnormal overall ECG results (46.7%), followed by participants in the impaired diabetic class (37.0%), then participants classified as normal (26.4%).

The prevalence of right bundle branch block increased significantly with age (p=0.001). Also significantly associated with right bundle branch block were occupation (p=0.040), lifetime cigarette smoking history (p=0.048), and diabetic class (p=0.001). Enlisted flyers had the highest prevalence of right bundle branch block (4.5%), followed by officers (2.6%), then enlisted groundcrew (1.9%). Heavy lifetime cigarette smokers had the highest prevalence of right bundle branch block (3.5%), followed by nonsmokers (2.2%), then moderate lifetime smokers (1.5%). Diabetic participants had the highest percentage of right bundle branch block (5.4%), followed by participants in the impaired diabetic class (2.6%), then participants classified as normal (1.9%).

The percentage of non-specific ST- and T-wave changes increased with age (p=0.001) and body fat (p=0.001), while decreasing with lifetime alcohol use (p=0.024). Family history of heart disease (p=0.001) and diabetic class (p=0.001) also were significant. Participants with a family history of heart disease had a higher percentage of non-specific ST- and T-wave changes than did participants with no history (21.1% versus 14.0%). Diabetic participants had the highest prevalence of non-specific ST- and T-wave changes (29.3%), followed by participants in the impaired diabetic class (24.5%), then participants classified as normal (14.6%).

The prevalence of bradycardia increased significantly with HDL cholesterol levels (p=0.043), while decreasing with the cholesterol-HDL ratio (p=0.005) and body fat (p=0.001). Occupation and diabetic class also were significantly related to bradycardia (p=0.001 each). Officers had the highest prevalence of bradycardia (5.6%), followed by enlisted flyers (3.0%), then enlisted groundcrew (1.8%). Participants in the normal diabetic class had the highest prevalence of bradycardia (4.5%), followed by diabetic participants (1.7%), then participants in the impaired diabetic class (0.4%).

Tachycardia was significantly associated with lifetime alcohol history (p=0.029) and diabetic class (p=0.008). Non-drinkers had the highest prevalence of tachycardia (1.7%), followed by heavy drinkers (0.8%), then moderate lifetime alcohol drinkers (0.2%). Diabetic participants had the highest prevalence of tachycardia (1.4%), followed by participants in the impaired diabetic class (0.4%), then participants classified as normal (0.2%).

The percentage of participants with arrhythmia increased with age (p=0.001).

Evidence of prior myocardial infarction from the ECG increased with age (p=0.001) and decreased with cholesterol levels (p=0.007). Lifetime cigarette smoking history (p=0.003) and diabetic class (p=0.001) also were significantly associated with prior myocardial infarction. Heavy lifetime cigarette smokers had the highest prevalence of a prior myocardial infarction (5.8%), followed by nonsmokers (2.9%), then moderate lifetime cigarette smokers (2.7%). Diabetic participants had the highest percentage of participants with evidence of a prior myocardial infarction (9.4%), followed by participants in the impaired diabetic class (5.1%), then participants classified as normal (2.8%).

The prevalence of abnormal funduscopic examination results increased with age (p=0.001), lifetime cigarette smoking history (p=0.001), and body fat (p=0.004). Occupation (p=0.001), current cigarette smoking (p=0.019), personality type (p=0.001), and diabetic class (p=0.001) were also significantly associated with an abnormal funduscopic examination. Enlisted flyers had the highest percentage of abnormal funduscopic examination results (18.6%), followed by enlisted groundcrew (11.5%), then officers (11.1%). Participants who never smoked had the lowest percentage of abnormal funduscopic exam results (8.9%), followed by participants who currently smoked up to 20 cigarettes per day (13.5%), former smokers (14.0%), and participants who currently smoked more than 20 cigarettes per day (14.1%). Abnormal funduscopic examinations were more prevalent for participants with personality type B than those with personality type A (14.4% versus 9.2%). Diabetic participants had the highest percentage of abnormal funduscopic exam results (20.0%), followed by participants in the impaired diabetic class (14.3%), then participants classified as normal (10.3%).

The percentage of participants with carotid bruits present increased with age (p=0.001) and lifetime cigarette smoking history (p=0.003). Current cigarette smoking and diabetic class also were significantly associated with carotid bruits (p=0.023 and p=0.007, respectively). Participants who currently smoked up to 20 cigarettes per day had the highest percentage of carotid bruits present (4.1%), followed by participants who currently smoked more than 20 cigarettes per day (3.7%), former smokers (3.1%), and participants who never smoked (1.0%). Diabetic participants had the highest prevalence of carotid bruits (5.1%), followed by participants in the impaired diabetic class (2.9%), then participants classified as normal (2.1%).

Tests of covariate association showed race (p=0.018), lifetime alcohol history (p=0.006), current alcohol use (p=0.005), and current cigarette smoking (p=0.010) to be significantly associated with abnormal radial pulses. The prevalence of abnormal results increased with lifetime alcohol use. Black participants had a higher percentage of abnormal radial pulses than non-Blacks (2.4% versus 0.4%). Participants who currently were moderate drinkers (in terms of drinks per day) had the highest percentage of abnormal radial pulses (1.6%), followed by light drinkers (0.3%), then participants who were the heaviest drinkers (0.0%). Participants who currently smoked up to 20 cigarettes per day had the highest percentage of abnormal radial pulses (1.9%), followed by participants who currently smoked more than 20 cigarettes per day (0.7%), former smokers (0.4%), and participants who never smoked (0.2%).

The prevalence of abnormal femoral pulses increased with age (p=0.009), lifetime alcohol history (p=0.002), and lifetime cigarette smoking history (p=0.002). Also significant were current alcohol use (p=0.001), current cigarette smoking (p=0.001), and diabetic class (p=0.003). Participants who were currently moderate drinkers had the highest percentage of abnormal femoral pulses (4.4%), followed by the heaviest drinkers (4.0%), then the light drinkers (1.0%). Participants who currently smoked up to 20 cigarettes per day had the highest percentage of abnormal femoral pulses (4.9%), followed by participants who currently smoked more than 20 cigarettes per day (4.4%), former smokers (1.2%), and participants who never smoked (0.3%). Diabetic participants had the highest percentage of abnormal femoral pulses (3.7%), followed by participants classified as normal (1.2%), then participants in the impaired diabetic class (1.1%).

The percentage of participants with abnormal popliteal pulses increased with age (p=0.001), lifetime alcohol history (p=0.013), current alcohol use (p=0.002), lifetime cigarette smoking history (p=0.001), and current cigarette smoking (p=0.001). The association with diabetic class also was significant (p=0.001). Participants who were currently moderate drinkers had the highest percentage of abnormal popliteal pulses (4.9%), followed by the heaviest drinkers (4.0%), then participants who were the lightest drinkers (1.9%). Participants who currently smoked up to 20 cigarettes per day had the highest percentage of abnormal popliteal pulses (7.1%), followed by participants who currently smoked more than 20 cigarettes per day (5.1%), former smokers (2.0%), and participants who never smoked (0.5%). Diabetic participants had the highest percentage of abnormal popliteal pulses (6.0%), followed by participants in the impaired diabetic class (1.8%), then participants classified as normal (1.7%).

The prevalence of abnormal dorsalis pedis pulses increased with age (p=0.001), lifetime cigarette smoking history (p=0.001), and current cigarette smoking (p=0.001). Lifetime alcohol history and diabetic class also were significant (p=0.009 and p=0.001, respectively). Heavy lifetime alcohol drinkers had the highest percentage of abnormal dorsalis pedis pulses (10.6%), followed by non-drinkers (8.5%), then moderate lifetime alcohol drinkers (6.6%). Diabetic participants had the highest prevalence of abnormal dorsalis pedis pulses (14.0%), followed by participants classified as normal (6.7%), then participants in the impaired diabetic class (5.5%).

The percentage of abnormal posterior tibial pulses increased with age (p=0.001), lifetime alcohol history (p=0.027), current alcohol use (p=0.003), lifetime cigarette smoking history (p=0.001), and current cigarette smoking (p=0.001). Personality type and diabetic class also were significantly associated with posterior tibial pulses (p=0.020 and p=0.001, respectively). Participants with type B personalities had more abnormal posterior tibial pulses than participants with type A personalities (6.7% versus 4.2%). Diabetic participants had the highest prevalence of abnormal posterior tibial pulses (13.4%), followed by participants in the impaired diabetic class (5.5%), then participants classified as normal (4.1%).

Abnormal leg pulses increased with age (p=0.001), lifetime cigarette smoking history (p=0.001), and current cigarette smoking (p=0.001). Occupation (p=0.044), lifetime alcohol history (p=0.013), and personality type (p=0.012) also were associated significantly with leg pulses. Enlisted flyers had the highest percentage of abnormal leg pulses (14.2%), followed by enlisted groundcrew (10.0%), then officers (9.3%). Heavy lifetime alcohol drinkers had the highest percentage of abnormal leg pulses (13.4%), followed by non-drinkers (11.0%), then moderate lifetime alcohol drinkers (9.0%). Participants with type B personalities had more abnormal leg pulses than participants with type A personalities (11.7% versus 8.2%). Diabetic participants had the highest prevalence of abnormal leg pulses (18.8%), followed by participants classified as normal (8.7%), then participants in the impaired diabetic class (8.4%).

The prevalence of abnormal peripheral pulses increased with age (p=0.001), lifetime cigarette smoking history (p=0.001), and current cigarette smoking (p=0.001), while decreasing with body fat (p=0.034). Lifetime alcohol history (p=0.005), current alcohol use (p=0.036), personality type (p=0.026), and diabetic class (p=0.001) also were associated significantly with abnormal peripheral pulses. Heavy lifetime alcohol drinkers had the highest percentage of abnormal peripheral pulses (14.0%), followed by non-drinkers (11.0%) and moderate lifetime alcohol drinkers (9.1%). Participants who were currently moderate drinkers had the highest percentage of abnormal peripheral pulses (14.2%), followed by the heaviest drinkers (14.0%), then participants who were the lightest drinkers (9.8%). Participants with type B personalities had a higher percentage of abnormal peripheral pulses than did participants with type A personalities (11.8% versus 8.7%). Diabetic participants had the highest prevalence of abnormal peripheral pulses (19.4%), followed by participants classified as normal (8.9%), then participants in the impaired diabetic class (8.4%).

The percentage of abnormal intermittent claudication and vascular insufficiency index (ICVI) results increased with lifetime cigarette smoking (p=0.001) and current cigarette smoking (p=0.001). Diabetic class was also significant (p=0.001). Diabetic participants had the highest percentage of abnormal ICVI results (9.1%), followed by participants in the impaired diabetic class (2.9%), then participants classified as normal (2.6%).

14.2.2 Exposure Analysis

The following section presents results of the statistical analysis of the dependent variables shown in Table 14-1. Dependent variables were derived from a medical records review and verification, physical examination and ECG determinations, and an ICVI index based on participant responses to three questions regarding leg pain.

Four models were examined for each dependent variable given in Table 14-1. 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 and Table 2-8, the average levels of exposure to dioxin were highest for enlisted groundcrew, followed by enlisted flyers, then officers.

Model 2 explored the relation between the dependent variable and an extrapolated initial dioxin measure for Ranch Hands who had a 1987 dioxin measurement greater than 10 ppt. If a participant did not have a 1987 dioxin level, the 1992 level was used to estimate the initial dioxin level. If a participant did not have a 1987 or a 1992 dioxin level, the 1997 level was used to estimate the initial dioxin level. A statistical adjustment for the percentage of body fat at the time of the participant's blood measurement of dioxin was included in this model to account for body-fat-related differences in elimination rate (52).

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.

14.2.2.1 Medical Records Variables

14.2.2.1.1 Essential Hypertension

All Model 1, 2, and 3 analyses of essential hypertension revealed no significant results (Table 14-3(a–f): $p>0.13$ for each analysis).

The unadjusted and adjusted Model 4 analyses each showed significant positive associations between essential hypertension and 1987 dioxin (Table 14-3(g,h): Est. RR=1.22, $p<0.001$; Adj. RR=1.18, $p=0.011$). The percentages of participants with essential hypertension in the low, medium, and high 1987 dioxin categories were 34.0, 38.0, and 49.1, respectively.

Table 14-3. Analysis of Essential Hypertension

(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED					
Occupational Category	**Group**	**n**	**Number (%) Yes**	**Est. Relative Risk (95% C.I.)**	**p-Value**
All	***Ranch Hand***	***850***	***345 (40.6)***	***0.95 (0.80,1.14)***	***0.606***
	Comparison	***1,220***	***509 (41.7)***		
Officer	Ranch Hand	329	128 (38.9)	0.90 (0.68,1.20)	0.467
	Comparison	480	199 (41.5)		
Enlisted Flyer	Ranch Hand	149	71 (47.7)	1.18 (0.77,1.83)	0.447
	Comparison	184	80 (43.5)		
Enlisted Groundcrew	Ranch Hand	372	146 (39.2)	0.92 (0.70,1.20)	0.519
	Comparison	556	230 (41.4)		

Table 14-3. Analysis of Essential Hypertension (Continued)

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	*0.96 (0.79,1.17)*	*0.708*
Officer	0.85 (0.63,1.16)	0.317
Enlisted Flyer	1.27 (0.79,2.04)	0.316
Enlisted Groundcrew	0.96 (0.72,1.29)	0.811

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

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Number (%) Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	152	65 (42.8)	1.06 (0.91,1.23)	0.441
Medium	160	72 (45.0)		
High	159	77 (48.4)		

[a] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[b] Relative risk for a twofold increase in initial dioxin.

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

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

	Analysis Results for Log_2 (Initial Dioxin)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
452	1.10 (0.91,1.32)	0.314

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

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED

Dioxin Category	n	Number (%) Yes	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,183	490 (41.4)		
Background RH	372	127 (34.1)	0.86 (0.67,1.11)	0.246
Low RH	229	94 (41.0)	0.95 (0.71,1.29)	0.758
High RH	242	120 (49.6)	1.22 (0.91,1.63)	0.177
Low plus High RH	471	214 (45.4)	1.08 (0.87,1.35)	0.488

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 14-3. Analysis of Essential Hypertension (Continued)

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

Dioxin Category	n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
Comparison	1,145		
Background RH	356	0.87 (0.66,1.14)	0.320
Low RH	217	0.87 (0.63,1.20)	0.395
High RH	235	1.27 (0.93,1.74)	0.131
Low plus High RH	452	1.06 (0.84,1.35)	0.624

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

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)	
1987 Dioxin	n	Number (%) Yes	Estimated Relative Risk (95% C.I.)[a]	p-Value
Low	282	96 (34.0)	1.22 (1.11,1.34)	<0.001
Medium	276	105 (38.0)		
High	285	140 (49.1)		

[a] Relative risk for a twofold increase in 1987 dioxin.

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

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED

	Analysis Results for Log_2 (1987 Dioxin + 1)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
808	1.18 (1.04,1.34)	0.011

[a] Relative risk for a twofold increase in 1987 dioxin.

14.2.2.1.2 Heart Disease (Excluding Essential Hypertension)

The unadjusted and adjusted Model 1 analyses of a history of heart disease each showed significant group differences when combining all occupations (Table 14-4(a,b): Est. RR=1.26, p=0.013; Adj. RR=1.26, p=0.018, respectively). The percentage of Ranch Hands with heart disease was 66.1 versus 60.8 percent for Comparisons. Stratifying by occupation, unadjusted and adjusted analyses revealed group differences within the enlisted flyer stratum (Table 14-4(a,b): Est. RR=2.10, p=0.003; Adj. RR=2.05; p=0.004, respectively). The percentage of Ranch Hand enlisted flyers with heart disease was 75.2 versus 59.7 percent for the Comparison enlisted flyers.

Table 14-4. Analysis of Heart Disease (Excluding Essential Hypertension)

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

Occupational Category	Group	n	Number (%) Yes	Est. Relative Risk (95% C.I.)	p-Value
All	*Ranch Hand*	*859*	*568 (66.1)*	*1.26 (1.05,1.51)*	*0.013*
	Comparison	*1,232*	*749 (60.8)*		
Officer	Ranch Hand	334	238 (71.3)	1.22 (0.90,1.66)	0.191
	Comparison	484	324 (66.9)		
Enlisted Flyer	Ranch Hand	149	112 (75.2)	2.10 (1.27,3.28)	0.003
	Comparison	186	111 (59.7)		
Enlisted Groundcrew	Ranch Hand	376	218 (58.0)	1.10 (0.84,1.42)	0.523
	Comparison	562	314 (55.9)		

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	*1.26 (1.04,1.53)*	*0.018*
Officer	1.21 (0.88,1.66)	0.238
Enlisted Flyer	2.10 (1.28,3.45)	0.004
Enlisted Groundcrew	1.10 (0.83,1.46)	0.496

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

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Number (%) Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	155	115 (74.2)	0.79 (0.68,0.91)	0.001
Medium	161	99 (61.5)		
High	160	88 (55.0)		

[a] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[b] Relative risk for a twofold increase in initial dioxin.

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

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

	Analysis Results for Log_2 (Initial Dioxin)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
457	0.90 (0.75,1.08)	0.249

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

Table 14-4. Analysis of Heart Disease (Excluding Essential Hypertension) (Continued)

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED				
Dioxin Category	**n**	**Number (%) Yes**	**Est. Relative Risk (95% C.I.)[ab]**	**p-Value**
Comparison	1,195	730 (61.1)		
Background RH	376	259 (68.9)	1.43 (1.11,1.83)	0.005
Low RH	233	163 (70.0)	1.48 (1.09,2.00)	0.011
High RH	243	139 (57.2)	0.84 (0.64,1.11)	0.228
Low plus High RH	476	302 (63.4)	1.11 (0.89,1.39)	0.359

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED			
Dioxin Category	**n**	**Adjusted Relative Risk (95% C.I.)[a]**	**p-Value**
Comparison	1,155		
Background RH	360	1.34 (1.03,1.75)	0.032
Low RH	221	1.33 (0.96,1.84)	0.081
High RH	236	1.03 (0.76,1.40)	0.865
Low plus High RH	457	1.16 (0.92,1.48)	0.209

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

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED				
1987 Dioxin Category Summary Statistics			**Analysis Results for Log_2 (1987 Dioxin + 1)**	
1987 Dioxin	**n**	**Number (%) Yes**	**Estimated Relative Risk (95% C.I.)[a]**	**p-Value**
Low	284	192 (67.6)	0.87 (0.79,0.96)	0.004
Medium	281	199 (70.8)		
High	287	170 (59.2)		

[a] Relative risk for a twofold increase in 1987 dioxin.

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

Table 14-4. Analysis of Heart Disease (Excluding Essential Hypertension) (Continued)

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (1987 Dioxin + 1)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
817	0.92 (0.81,1.04)	0.159

[a] Relative risk for a twofold increase in 1987 dioxin.

The unadjusted Model 2 analysis revealed a significant inverse association between heart disease and initial dioxin (Table 14-4(c): Est. RR=0.79, p=0.001). The percentages of participants with heart disease in the low, medium, and high initial dioxin categories were 74.2, 61.5, and 55.0, respectively. After covariate adjustment, the results became nonsignificant (Table 14-4(d): p=0.249).

The Model 3 unadjusted analysis of heart disease revealed two significant contrasts: Ranch Hands in the background dioxin category versus Comparisons and Ranch Hands in the low dioxin category versus Comparisons (Table 14-4(e): Est. RR=1.43, p=0.005; Est. RR=1.48, p=0.011, respectively). The adjusted analysis showed a significant difference between Ranch Hands in the background dioxin category and Comparisons (Table 14-4(f): Adj. RR=1.34, p=0.032) and a marginally significant difference between Ranch Hands in the low dioxin category and Comparisons (Table 14-4(f): Adj. RR=1.33, p=0.081). The percentages of participants with heart disease for Ranch Hands in the background dioxin category, Ranch Hands in the low dioxin category, and Comparisons were 68.9, 70.0, and 61.1, respectively.

The Model 4 unadjusted analysis showed a significant inverse association between heart disease and 1987 dioxin (Table 14-4(g): Est. RR=0.87, p=0.004). The percentages of participants with heart disease in the low, medium, and high 1987 dioxin categories were 67.6, 70.8, and 59.2, respectively. The results became nonsignificant after adjusting for covariates (Table 14-4(h): p=0.159).

14.2.2.1.3 Myocardial Infarction

All unadjusted and adjusted Model 1 through Model 4 analyses of myocardial infarction were nonsignificant (Table 14-5(a–h): p>0.10 for each analysis).

Table 14-5. Analysis of Myocardial Infarction

(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED					
Occupational Category	Group	n	Number (%) Yes	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***859***	***74 (8.6)***	***1.04 (0.76,1.43)***	***0.786***
	Comparison	***1,232***	***102 (8.3)***		
Officer	Ranch Hand	334	28 (8.4)	0.96 (0.58,1.59)	0.882
	Comparison	484	42 (8.7)		
Enlisted Flyer	Ranch Hand	149	16 (10.7)	1.37 (0.65,2.87)	0.403
	Comparison	186	15 (8.1)		
Enlisted Groundcrew	Ranch Hand	376	30 (8.0)	1.00 (0.62,1.61)	0.987
	Comparison	562	45 (8.0)		

Table 14-5. Analysis of Myocardial Infarction (Continued)

(b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED		
Occupational Category	**Adjusted Relative Risk (95% C.I.)**	**p-Value**
All	*1.02 (0.73,1.42)*	*0.915*
Officer	0.86 (0.50,1.46)	0.567
Enlisted Flyer	1.57 (0.72,3.43)	0.255
Enlisted Groundcrew	0.99 (0.59,1.67)	0.975

(c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED				
Initial Dioxin Category Summary Statistics			**Analysis Results for Log₂ (Initial Dioxin)[a]**	
Initial Dioxin	**n**	**Number (%) Yes**	**Estimated Relative Risk (95% C.I.)[b]**	**p-Value**
Low	155	12 (7.7)	1.01 (0.79,1.28)	0.945
Medium	161	18 (11.2)		
High	160	13 (8.1)		

[a] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[b] Relative risk for a twofold increase in initial dioxin.

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

(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (Initial Dioxin)	
n	**Adjusted Relative Risk (95% C.I.)[a]**	**p-Value**
457	1.30 (0.95,1.77)	0.106

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

Note: Results are not adjusted for race because of the sparse number of participants with a myocardial infarction.

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED				
Dioxin Category	**n**	**Number (%) Yes**	**Est. Relative Risk (95% C.I.)[ab]**	**p-Value**
Comparison	1,195	98 (8.2)		
Background RH	376	29 (7.7)	0.98 (0.63,1.51)	0.919
Low RH	233	19 (8.2)	0.99 (0.59,1.65)	0.958
High RH	243	24 (9.9)	1.18 (0.73,1.89)	0.496
Low plus High RH	476	43 (9.0)	1.08 (0.74,1.58)	0.689

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 14-5. Analysis of Myocardial Infarction (Continued)

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED			
Dioxin Category	**n**	**Adjusted Relative Risk (95% C.I.)[a]**	**p-Value**
Comparison	1,155		
Background RH	360	0.89 (0.55,1.43)	0.625
Low RH	221	0.84 (0.49,1.46)	0.544
High RH	236	1.39 (0.83,2.32)	0.215
Low plus High RH	457	1.09 (0.73,1.63)	0.673

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

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED				
1987 Dioxin Category Summary Statistics			**Analysis Results for Log_2 (1987 Dioxin + 1)**	
1987 Dioxin	**n**	**Number (%) Yes**	**Estimated Relative Risk (95% C.I.)[a]**	**p-Value**
Low	284	21 (7.4)	1.03 (0.87,1.21)	0.740
Medium	281	23 (8.2)		
High	287	28 (9.8)		

[a] Relative risk for a twofold increase in 1987 dioxin.

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

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (1987 Dioxin + 1)	
n	**Adjusted Relative Risk (95% C.I.)[a]**	**p-Value**
817	1.16 (0.94,1.44)	0.170

[a] Relative risk for a twofold increase in 1987 dioxin.

14.2.2.1.4 Stroke or Transient Ischemic Attack

All analysis results of stroke or transient ischemic attack were nonsignificant (Table 14-6(a–h): p≥ 0.10 for each analysis).

Table 14-6. Analysis of Stroke or Transient Ischemic Attack

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

Occupational Category	Group	n	Number (%) Yes	Est. Relative Risk (95% C.I.)	p-Value
All	*Ranch Hand*	*859*	*11 (1.3)*	*1.13 (0.51,2.50)*	*0.766*
	Comparison	*1,232*	*14 (1.1)*		
Officer	Ranch Hand	334	5 (1.5)	1.46 (0.42,5.07)	0.555
	Comparison	484	5 (1.0)		
Enlisted Flyer	Ranch Hand	149	0 (0.0)	--	0.330[a]
	Comparison	186	3 (1.6)		
Enlisted Groundcrew	Ranch Hand	376	6 (1.6)	1.50 (0.48,4.69)	0.483
	Comparison	562	6 (1.1)		

[a] P-value determined using a chi-square test with continuity correction because of the sparse number of participants with a stroke or transient ischemic attack.

--: Results not presented because of the sparse number of participants with a stroke or transient ischemic attack.

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	*1.21 (0.51,2.85)*	*0.666*
Officer	1.18 (0.31,4.51)	0.806
Enlisted Flyer	--	--
Enlisted Groundcrew	1.80 (0.53,6.06)	0.345

--: Results not presented because of the sparse number of participants with a stroke or transient ischemic attack.

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

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Number (%) Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	155	1 (0.6)	1.22 (0.68,2.16)	0.513
Medium	161	2 (1.2)		
High	160	3 (1.9)		

[a] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[b] Relative risk for a twofold increase in initial dioxin.

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

Table 14-6. Analysis of Stroke or Transient Ischemic Attack (Continued)

(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (Initial Dioxin)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
457	1.33 (0.72,2.47)	0.379

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

Note: Results are not adjusted for race and occupation because of the sparse number of Ranch Hands with a stroke or transient ischemic attack.

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED				
Dioxin Category	n	Number (%) Yes	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,195	14 (1.2)		
Background RH	376	5 (1.3)	1.13 (0.40,3.18)	0.816
Low RH	233	1 (0.4)	0.36 (0.05,2.78)	0.330
High RH	243	5 (2.1)	1.78 (0.63,5.02)	0.275
Low plus High RH	476	6 (1.3)	0.82 (0.25,2.68)	0.741

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED			
Dioxin Category	n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
Comparison	1,155		
Background RH	360	0.97 (0.30,3.16)	0.956
Low RH	221	0.42 (0.05,3.26)	0.404
High RH	236	2.65 (0.83,8.46)	0.100
Low plus High RH	457	1.08 (0.32,3.71)	0.900

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

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 14-6. Analysis of Stroke or Transient Ischemic Attack (Continued)

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED				
1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)	
1987 Dioxin	n	Number (%) Yes	Estimated Relative Risk (95% C.I.)[a]	p-Value
Low	284	4 (1.4)	0.99 (0.66,1.48)	0.957
Medium	281	2 (0.7)		
High	287	5 (1.7)		

[a] Relative risk for a twofold increase in 1987 dioxin.

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

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (1987 Dioxin + 1)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
817	1.15 (0.71,1.85)	0.578

[a] Relative risk for a twofold increase in 1987 dioxin.

Note: Results are not adjusted for occupation because of the sparse number of Ranch Hands with a stroke or transient ischemic attack.

14.2.2.2 Physical Examination Variables – Central Cardiac Function

14.2.2.2.1 Systolic Blood Pressure (Continuous)

All Model 1 and Model 2 analyses of systolic blood pressure in its continuous form showed no significant results (Table 14-7(a–d): p>0.23 for each analysis).

Table 14-7. Analysis of Systolic Blood Pressure (Continuous)

(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED					
Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***859***	***124.9***	***–0.7 --***	***0.383***
	Comparison	***1,232***	***125.6***		
Officer	Ranch Hand	334	125.9	–0.2 --	0.865
	Comparison	484	126.2		
Enlisted Flyer	Ranch Hand	149	127.0	–0.3 --	0.875
	Comparison	186	127.3		
Enlisted Groundcrew	Ranch Hand	376	123.1	–1.4 --	0.241
	Comparison	562	124.5		

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

Table 14-7. Analysis of Systolic Blood Pressure (Continuous) (Continued)

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

Occupational Category	Group	n	Adjusted Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]
All	*Ranch Hand*	*822*	*127.7*	*–0.6 --*	*0.415*
	Comparison	*1,189*	*128.4*		
Officer	Ranch Hand	322	127.2	–0.9 --	0.468
	Comparison	472	128.1		
Enlisted Flyer	Ranch Hand	140	128.7	0.1 --	0.967
	Comparison	178	128.6		
Enlisted Groundcrew	Ranch Hand	360	127.5	–0.7 --	0.574
	Comparison	539	128.2		

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

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

Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	155	125.8	126.4	0.049	–0.006 (0.005)	0.238
Medium	161	125.7	125.8			
High	160	124.2	123.6			

[a] Transformed from natural logarithm scale.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[c] Slope and standard error based on natural logarithm of systolic blood pressure versus $\log_2$ (initial dioxin).

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

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

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)		
Initial Dioxin	n	Adj. Mean[a]	R^2	Adj. Slope (Std. Error)[b]	p-Value
Low	150	129.0	0.135	–0.000 (0.006)	0.983
Medium	150	130.2			
High	157	128.5			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of systolic blood pressure versus $\log_2$ (initial dioxin).

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

Table 14-7. Analysis of Systolic Blood Pressure (Continuous) (Continued)

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED

Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	1,195	125.6	125.5		
Background RH	376	124.4	125.4	–0.1 --	0.935
Low RH	233	126.2	125.9	0.4 --	0.730
High RH	243	124.4	123.4	–2.1 --	0.079
Low plus High RH	476	125.2	124.6	–0.9 --	0.346

[a] Transformed from natural logarithm scale.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[d] P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

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

Dioxin Category	n	Adj. Mean[a]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[b]	p-Value[c]
Comparison	1,155	128.5		
Background RH	360	128.5	0.0 --	0.990
Low RH	221	127.9	–0.6 --	0.651
High RH	236	127.0	–1.5 --	0.222
Low plus High RH	457	127.4	–1.1 --	0.262

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 14-7. Analysis of Systolic Blood Pressure (Continuous) (Continued)

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED					
1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin +1)		
1987 Dioxin	n	Mean[a]	R^2	Slope (Std. Error)[b]	p-Value
Low	284	124.0	<0.001	0.001 (0.003)	0.693
Medium	281	125.9			
High	287	124.8			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of systolic blood pressure versus $\log_2$ (1987 dioxin + 1).

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

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED					
1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)		
1987 Dioxin	n	Adj. Mean[a]	R^2	Adjusted Slope (Std. Error)[b]	p-Value
Low	271	128.3	0.126	–0.005 (0.004)	0.165
Medium	271	127.2			
High	275	127.1			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of systolic blood pressure versus $\log_2$ (1987 dioxin + 1).

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

The unadjusted Model 3 analysis showed a marginally significant difference between Ranch Hands in the high dioxin category and Comparisons (Table 14-7(e): difference of means=–2.1 mm Hg, p=0.079). Ranch Hands in the high dioxin category had a lower mean systolic blood pressure (123.4 mm Hg) than the Comparisons (125.5 mm Hg). The adjusted Model 3 analysis revealed no significant contrasts (Table 14-7(f): p>0.22 for each contrast).

Both the unadjusted and adjusted Model 4 analyses revealed no significant associations between 1987 dioxin and systolic blood pressure in its continuous form (Table 14-7(g,h): p>0.16 for each analysis).

14.2.2.2.2 Systolic Blood Pressure (Discrete)

The unadjusted and adjusted Model 1 analyses of systolic blood pressure in its discrete form showed no significant differences between Ranch Hands and Comparisons when examined across all occupations and within each occupation (Table 14-8(a,b): p>0.63 for each contrast).

Table 14-8. Analysis of Systolic Blood Pressure (Discrete)

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

Occupational Category	Group	n	Number (%) High	Est. Relative Risk (95% C.I.)	p-Value
All	*Ranch Hand*	*859*	*181 (21.1)*	*0.99 (0.80,1.22)*	*0.914*
	Comparison	*1,232*	*262 (21.3)*		
Officer	Ranch Hand	334	78 (23.4)	1.01 (0.73,1.41)	0.944
	Comparison	484	112 (23.1)		
Enlisted Flyer	Ranch Hand	149	36 (24.2)	1.06 (0.64,1.76)	0.823
	Comparison	186	43 (23.1)		
Enlisted Groundcrew	Ranch Hand	376	67 (17.8)	0.92 (0.66,1.29)	0.638
	Comparison	562	107 (19.0)		

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	*0.99 (0.79,1.24)*	*0.899*
Officer	0.95 (0.67,1.35)	0.784
Enlisted Flyer	1.13 (0.66,1.93)	0.661
Enlisted Groundcrew	0.96 (0.67,1.38)	0.832

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

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Number (%) High	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	155	40 (25.8)	0.83 (0.69,0.99)	0.031
Medium	161	36 (22.4)		
High	160	29 (18.1)		

[a] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[b] Relative risk for a twofold increase in initial dioxin.

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

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

	Analysis Results for Log_2 (Initial Dioxin)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
457	0.89 (0.71,1.11)	0.296

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

Table 14-8. Analysis of Systolic Blood Pressure (Discrete) (Continued)

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED

Dioxin Category	n	Number (%) High	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,195	253 (21.2)		
Background RH	376	74 (19.7)	1.00 (0.75,1.34)	0.998
Low RH	233	59 (25.3)	1.25 (0.90,1.73)	0.188
High RH	243	46 (18.9)	0.80 (0.56,1.14)	0.208
Low plus High RH	476	105 (22.1)	0.99 (0.76,1.29)	0.952

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

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

Dioxin Category	n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
Comparison	1,155		
Background RH	360	1.00 (0.73,1.37)	0.983
Low RH	221	1.12 (0.79,1.59)	0.532
High RH	236	0.84 (0.57,1.23)	0.365
Low plus High RH	457	0.96 (0.73,1.27)	0.791

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

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)	
1987 Dioxin	n	Number (%) High	Estimated Relative Risk (95% C.I.)[a]	p-Value
Low	284	54 (19.0)	1.00 (0.89,1.12)	0.956
Medium	281	66 (23.5)		
High	287	59 (20.6)		

[a] Relative risk for a twofold increase in 1987 dioxin.

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

Table 14-8. Analysis of Systolic Blood Pressure (Discrete) (Continued)

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (1987 Dioxin + 1)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
817	0.88 (0.76,1.02)	0.099

[a] Relative risk for a twofold increase in 1987 dioxin.

A significant inverse association between discrete systolic blood pressure and initial dioxin was found in the unadjusted Model 2 analysis (Table 14-8(c): Est. RR=0.83, p=0.031). After adjusting for covariates, the results became nonsignificant (Table 14-8(d): p=0.296).

The unadjusted and adjusted Model 3 analyses of systolic blood pressure showed no significant contrasts between the Ranch Hand dioxin category and Comparisons (Table 14-8(e,f): p>0.18 for each contrast).

The unadjusted Model 4 results were nonsignificant (Table 14-8(g): p=0.956). After adjusting for covariates, the results became marginally significant (Table 14-8(h): Adj. RR=0.88, p=0.099). The percentages of participants with high discrete systolic blood pressures in the low, medium, and high 1987 dioxin categories were 19.0, 23.5, and 20.6, respectively.

14.2.2.2.3 Diastolic Blood Pressure (Continuous)

All Model 1 and Model 2 analyses of diastolic blood pressure in its continuous form showed no significant results (Table 14-9(a–d): p≥0.19 for each analysis).

The unadjusted Model 3 analysis of continuous diastolic blood pressure revealed a marginally significant difference between Ranch Hands in the high dioxin category and Comparisons (Table 14-9(e): difference of means=1.08 mm Hg, p=0.099). The adjusted results were nonsignificant (Table 14-9(f): p>0.13 for each contrast).

A significant positive association between 1987 dioxin and continuous diastolic blood pressure was found in the unadjusted Model 4 analysis (Table 14-9(g): slope=0.031, p=0.014). The mean diastolic blood pressure in the low, medium, and high 1987 dioxin categories was 73.97 mm Hg, 73.76 mm Hg, and 75.94 mm Hg, respectively. After adjusting for covariates, the results became nonsignificant (Table 14-9(h): p=0.315).