CHAPTER 12

CARDIOVASCULAR ASSESSMENT

INTRODUCTION

Background

Cardiovascular disease is not recognized as a clinical endpoint associated with exposure to phenoxy herbicides, chlorophenols, or dioxin. At present, there is no evidence that humans experience chronic cardiovascular sequelae related to low-dose exposure.

Much recent animal research into the cardiotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has focused on acute biochemical and functional abnormalities associated with high-level exposure. In one study (1), rats were found to have significant reductions in pulse and blood pressure 6 days after administration of 40 μg/kg of TCDD by gavage and were less responsive to the chronotropic effects of isoproterenol, a beta-agonist. The authors of the study, noting a 66 percent reduction in serum thyroxin, 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, 3). Experiments into the effects of TCDD on myocardial contractility in rat (4) and guinea pig (5) atrial muscle have yielded mixed results; the primary cardiotoxic effects remain unclear.

The biochemical effects of TCDD 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 subsequent to TCDD administration (1). Dose-dependent decreases in adipose tissue lipoprotein lipase activity and hepatic low-density lipoprotein binding occurred in rabbits exposed to TCDD (6). In association with a concomitant increase in serum cholesterol and triglycerides, electron microscopic studies have documented pre-atherosclerotic lesions in the aortic arch. The relevance of these findings to the development of arteriosclerosis in humans is doubtful.

Human case reports and epidemiologic studies have not detected significant cardiac abnormalities following exposure to herbicides or TCDD. In three case reports of acute 2,4-D poisoning, cardiac dilation and cardiac arrest were observed in the one fatal case (7), while transient nodal tachycardia was observed in one of the two nonfatal cases (8, 9). Three laboratory technicians with chloracne, neurological symptoms, and hypercholesterolemia following significant direct exposure to TCDD did not manifest any cardiac dysfunction (10); however, of 10 industrial workers with chloracne, 4 complained of heart palpitations and shortness of breath (11). In other studies involving 128 industrial workers, no excess of cardiac complaints or findings was noted (12, 13, 14). Intoxication of a 51-year-old man with 2,4-D was shown to prolong the Q-T interval in an electrocardiogram (ECG); coma was also induced (15).

In recent reports of the 1976 Seveso, Italy, accident, an increased mortality from cardiovascular causes was noted but thought to be more likely related to other risk factors,

particularly the situational stress associated with exposure to TCDD (16, 17). In addition, two contemporary epidemiologic studies using similar cohorts from a Nitro, West Virginia, chemical plant detected no significant cardiac impairments in exposed workers (18, 19). However, one study found significantly lower levels of high-density lipoprotein (HDL) cholesterol in individuals with chloracne, as contrasted to individuals without chloracne (19). Two recent clinical-epidemiologic pilot studies of residential areas in Missouri which were contaminated by TCDD did not disclose any significant cardiac disease in exposed residents (20, 21), although the Times Beach Study noted diminished peripheral pulses in the exposed group, as did the Baseline Air Force Health Study (AFHS). The 1985 AFHS examination found group differences of borderline significance in verified heart disease that were not supported by other objective cardiovascular indices (22). More detailed summaries of the pertinent scientific literature for the cardiovascular assessment can be found in the report of the previous analyses of the 1987 examination data (23).

Summary of Previous Analyses of the 1987 Examination Data

The cardiovascular evaluation was based on reported and verified heart disease (essential hypertension, overall heart disease, and myocardial infarction) and measurement of central cardiac function and peripheral vascular function in Ranch Hands and Comparisons. Based on reported and verified hypertension and heart disease, the health of the two groups was similar. For reported/verified myocardial infarction, there was a statistically significant difference in the relative risk with family history of heart disease. The relative risk was less than 1 in those with no family history of heart disease and greater than 1 in those with a family history of heart disease, although neither of these within-stratum relative risks was statistically significant. 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 had arrhythmias (marginally significant).

There were differences in the relative risk with levels of covariates for systolic blood pressure and nonspecific ST and T waves, but none of the relative risks was statistically significant in any particular stratum of individuals. For the peripheral vascular function, significant or marginally significant differences were detected for five of the eight measurements. The Ranch Hands had a higher or marginally higher mean or percent abnormal for diastolic blood pressure (continuous), carotid bruits, femoral pulses, and dorsalis pedis pulses than did the 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 the Comparisons than in the Ranch Hands. On the three pulse indices (leg, peripheral, and all pulses), the Ranch Hands had marginally or significantly higher percentages of abnormalities than the Comparisons. Arterial occlusive disease is often unilateral rather than bilateral and can affect large vessels proximally or smaller vessels distally in segmental fashion. Distal circulation may be maintained by good collateral vessels even in the presence of proximal, partial pulse deficits. The Doppler should be more reliable than palpation in such cases, but neither method is perfect. The peripheral pulses were measured by manual palpation in the 1987 examination and at Baseline, when differences were also detected. In the 1985 examination, pulses were assessed manually and by the Doppler technique; the two groups were found to be similar at that time. Longitudinal analysis of ECG findings did not indicate excess cardiovascular risk in the Ranch Hands.

Parameters for the Cardiovascular Assessment

Dependent Variables

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

Questionnaire Data

During the Baseline, 1985, and 1987 health interviews, each participant was asked if he had a heart condition. Medical records were sought on all individuals to verify reported conditions and to determine the time of occurrence of major cardiac events (including cardiovascular death). In addition, the review-of-systems portion of the physical examination recorded the overall history of heart trouble and other serious illnesses.

Based on the self-reported information and subsequent verification, three conditions, each classified as yes or no, were analyzed: essential hypertension, heart disease (excluding essential hypertension), and myocardial infarction. Heart disease was analyzed, as reported and as verified by medical records. For essential hypertension and myocardial infarction, each of the reported conditions was verified. Participants with a verified history of diabetes or a 2-hour postprandial glucose level of 200 mg/dl or more were excluded from the primary analyses of reported and verified essential hypertension, heart disease, and myocardial infarction. As seen in Chapter 15, Endocrine Assessment, a post-Southeast Asia (SEA) history of diabetes was associated with dioxin. Participants with a verified pre-SEA heart condition were also excluded from all analyses. An additional analysis was done on diabetics only for myocardial infarction.

Physical Examination Data

Cardiovascular data analyzed from the 1987 physical examination were divided into two main categories: central cardiac function and peripheral vascular function.

Central Cardiac Function

The assessment of the central cardiac function at the cardiovascular examination was made by measurements of systolic blood pressure, heart sounds (by auscultation), and an ECG. Systolic blood pressure was determined by an automated electronic monitor with the nondominant arm placed at heart level; the systolic pressure corresponding to the lowest diastolic value of three readings was 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 internist examiners to be functional (normal) or organic (abnormal) in nature. ECG's were obtained after adherence to a 4-hour abstinence from tobacco. The standard 12-lead ECG was performed and an additional strip in lead-II was produced if any deviation from normal was found. The following items were considered to be abnormal: right bundle branch block (RBBB), left bundle branch block (LBBB), nonspecific ST- and T-wave changes, bradycardia (a resting pulse rate less than 50 beats per minute), tachycardia, arrhythmia (any irregularity of heart rhythm including premature

beats but excluding normal sinus rhythm), and other diagnoses (e.g., arteriovenous block, evidence of a prior myocardial infarction, Wolfe-Parkinson White syndrome).

Variables analyzed in the evaluation of the central cardiac function included systolic blood pressure, heart sounds, and eight conditions associated with the ECG. An overall assessment of the ECG was analyzed, as well as the individual conditions of RBBB, LBBB, nonspecific ST- and T-wave changes, bradycardia, tachycardia, arrhythmia, and other diagnoses. Systolic blood pressure was analyzed as a continuous variable and also as a discrete variable, classified as normal (≤140 mm Hg) and abnormal (>140 mm Hg). All other variables were dichotomized as normal/abnormal.

Only one Comparison and no Ranch Hands were diagnosed as having tachycardia; consequently, no analyses were performed on this cardiovascular endpoint.

Participants with a verified history of diabetes or a 2-hour postprandial glucose level of 200 mg/dl or more were excluded from the analyses of the central cardiac function variables. Participants with a verified pre-SEA heart condition were also excluded from all analyses.

Peripheral Vascular Function

The peripheral vascular function was assessed during the cardiovascular examination by the diastolic blood pressure; funduscopic examination of small vessels; the presence or absence of carotid bruits; and manual palpation of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Diastolic blood pressure was measured by an automated electronic monitor. The recorded value represents the lowest diastolic value of three readings. Elevated diastolic blood pressure is an indicator of incomplete diffusion of the stroke output throughout the peripheral arterial system. The funduscopic examination was conducted with undilated pupils in a standard manner, with emphasis placed upon the detection of arteriovenous nicking (a sign of chronic blood pressure elevation), hemorrhages, exudate, and papilledema. The presence or absence of carotid bruits was assessed by auscultation over both carotid arteries.

Diastolic blood pressure was analyzed as both a continuous and discrete variable, dichotomized as normal (≤90 mm Hg) and abnormal (>90 mm Hg). The funduscopic examination, carotid bruits, and the five pulses were also dichotomized as abnormal/normal (or presence/absence) and analyzed. Pulses were considered abnormal if diminished or absent on either side. In addition, three 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
- All pulses: radial, femoral, popliteal, dorsalis pedis, posterior tibial, and carotid pulses.

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

Participants with a verified history of diabetes or a 2-hour postprandial glucose level of 200 mg/dl or more were excluded from the primary analyses of the peripheral vascular function variables. Post-SEA history of diabetes was positively associated with dioxin. Analyses were performed on diabetics only for leg pulses. Individuals with peripheral edema were excluded from the analysis of the individual peripheral pulses, in addition to analysis of the components of the three indices involving peripheral pulses. Participants with a verified pre-SEA heart condition were also excluded from all analyses.

Covariates

A number of covariates were examined in the adjusted analyses of the cardiovascular assessment. Many of these covariates are considered to be classical risk factors for CHD. Covariates examined included age, race, lifetime cigarette smoking history, current level of cigarette smoking, lifetime alcohol history, current alcohol use, cholesterol, HDL, cholesterol-HDL ratio, percent body fat, personality type, differential cortisol response, family history of heart disease, and family history of heart disease before the age of 50. Personality type was determined from the Jenkins Activity Survey administered during the 1985 examination, and differential cortisol response was determined from laboratory results from the 1985 laboratory examination. Family history of heart disease was defined as "yes" if the participant's brother(s) or father died of heart disease or a heart attack and "no" otherwise. Family history of heart disease before the age of 50 was defined as "yes" if the participant's brother(s) or father died of heart disease or a heart attack before his 50th birthday and "no" otherwise.

Due to the large number of candidate covariates and certain covariates being highly correlated, only one variable from each of the following sets was selected for use as a candidate covariate: (1) lifetime cigarette smoking history and current level of cigarette smoking; (2) lifetime alcohol history and current alcohol use; (3) cholesterol, HDL, and the cholesterol-HDL ratio; and (4) family history of heart disease and family history of heart disease before the age of 50.

Preliminary analyses found the lifetime smoking and alcohol history variables to be more highly associated with dioxin (thus, possible confounders) than the current smoking and current alcohol variables. The lifetime smoking and alcohol history variables are also believed to be more important as clinical cardiovascular risk factors than the current use for these habits. Neither the family history of heart disease nor the family history of heart disease before the age of 50 was significantly associated with dioxin. Both variables are considered medically important risk factors for coronary heart disease; however, the occurrence of heart disease at a young age is relatively rare. Only 3.4 percent of the participants in the cardiovascular assessment had a history of family heart disease before the age of 50 as opposed to 23.1 percent with a family history of heart disease, supporting the choice of the latter variable as a candidate covariate. All three cholesterol variables (cholesterol, HDL, and the cholesterol-HDL ratio) were significantly associated with dioxin when adjusted for age; however, medical opinion deemed total cholesterol the most relevant variable for the cardiovascular assessment.

Therefore, the preliminary analyses of the possible confounding effects of the covariates, in conjunction with medical opinion, led to the development of a subset of covariates for use in

the adjusted analyses, which contained lifetime cigarette smoking history, lifetime alcohol history, family history of heart disease, and total cholesterol.

Participants at the 1987 examination who did not attend the 1985 examination had missing information for personality type and differential cortisol response. Individuals on corticosteroids in 1985 were excluded from analyses adjusting for differential cortisol, and individuals with fever ($\geq 100^{\circ}$F) or a positive hepatitis B surface antigen test were excluded from analyses adjusting for cholesterol.

Relation to Baseline, 1985, and 1987 Studies

The evaluation of the cardiovascular examination in this report was quite similar to the three previous studies. The family history of heart disease and family history of heart disease before the age of 50 covariates were added for the 1987 study and the serum dioxin analysis.

The cardiovascular longitudinal analyses focused on the overall ECG diagnosis, where group differences in the changes from Baseline to the 1987 examination were analyzed for this variable.

Statistical Methods

Three statistical models were used to examine the association between a cardiovascular endpoint dependent variable and serum dioxin levels. One model related a dependent variable to each Ranch Hand's initial dioxin value (extrapolated from current dioxin values using a first-order pharmacokinetic model). A second model related a dependent variable to each Ranch Hand's current serum dioxin value and each Ranch Hand's time since tour. The phrase "time since tour" is often referred to as "time" in discussions of these results. Both of these models were implemented under the minimal and maximal assumptions (i.e., Ranch Hands with current dioxin above 10 ppt and above 5 ppt, respectively). The third model compared the cardiovascular endpoint dependent variable for Ranch Hands having current dioxin values categorized as unknown, low, and high with Comparisons having background levels. The contrast of the entire Ranch Hand group with the complete Comparison group can be found in the previous report of analyses of the 1987 examination (23). All three models were implemented with and without covariate adjustment. Chapter 4, Statistical Methods, provides a more detailed discussion of the models.

As noted in the Endocrine Assessment, there was a significant positive association between diabetes and dioxin. This association does not affect the analyses of this chapter because only non-diabetics were analyzed, but it precludes investigation of a dioxin-by-diabetes interaction. Additional analyses (unadjusted and adjusted for age) were performed on diabetics only for myocardial infarction and leg pulses. The association between diabetes and dioxin will be evaluated in future cycles of the AFHS.

The modeling strategy was modified for the adjusted analyses of the cardiovascular endpoints. For these variables, only the covariate main effects and dioxin-by-covariate interactions (Appendix Table K-1) were examined; the pairwise covariate interactions were not investigated due to the large number of covariates.

In addition, percent body fat and cholesterol exhibited a significant positive association with dioxin (see Chapter 6, General Health Assessment, and Chapter 10, Gastrointestinal Assessment, respectively). Consequently, clinical endpoints in the cardiovascular assessment may be related to dioxin due to the association between dioxin and cholesterol and/or dioxin and percent body fat. To investigate this possibility, the dioxin effect was evaluated in the context of two models whenever cholesterol and/or percent body fat were retained in the final model. The results of the analysis adjusting for cholesterol and/or percent body fat are tabled and discussed in the text. Appendix Table K-2 presents additional results for the final model excluding cholesterol and/or percent body fat. If the final model included a dioxin-by-covariate interaction, Appendix Table K-3 shows stratified results for the interaction model without adjustment for cholesterol and/or percent body fat. In general, these followup analyses are only discussed in the text if a change in the significance of the results occurred.

Table 12-1 summarizes the statistical analyses performed for the cardiovascular examination. The first part of this table describes the dependent variables to be analyzed. The second part of this table provides a further description of candidate covariates to be examined. Abbreviations are used extensively in the body of the table and are defined in footnotes.

Table 12-2 provides a list of the number of participants excluded and the reasons for exclusion as well as the number of participants with missing data for the dependent variables and covariates described in Table 12-1.

Appendix K contains graphic displays of cardiovascular endpoint dependent variables versus initial dioxin for the minimal and maximal Ranch Hands cohorts, and cardiovascular endpoint variables versus current dioxin for Ranch Hands and Comparisons. Appendix K also displays graphics for dioxin-by-covariate interactions determined by various statistical models. A guide to assist in interpreting the graphics is found in Chapter 4.

RESULTS

Exposure Analysis

Questionnaire Variables

Reported/Verified Essential Hypertension

All cases of reported hypertension were verified; therefore, these two endpoints were analyzed as a single variable: reported/verified hypertension. This variable will be referred to as essential hypertension.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, essential hypertension was not associated significantly with initial dioxin under the minimal assumption (Table 12-3 [a]: p=0.300). However, the unadjusted maximal analysis displayed a marginally significant positive relationship between initial dioxin and essential hypertension (Table 12-3 [b]: Est. RR=1.11, p=0.098). The

TABLE 12-1.

Statistical Analysis for the Cardiovascular Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Reported Essential Hypertension	Q/PE-SR	D	Yes No	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR
Verified Essential Hypertension	Q/PE-V	D	Yes No	AGE,RACE, PACKYR, ALC,DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR
Reported Heart Disease (Excluding Essential Hypertension)	Q/PE-SR	D	Yes No	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR
Verified Heart Disease (Excluding Essential Hypertension)	Q/PE-V	D	Yes No	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR

TABLE 12-1. (Continued)

Statistical Analysis for the Cardiovascular Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Reported Myocardial Infarction	Q/PE-SR	D	Yes No	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR,FT
Verified Myocardial Infarction	Q/PE-V	D	Yes No	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR,FT
Systolic Blood Pressure (mm Hg)	PE	D/C	Abnormal: >140 Normal: ≤140	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR,GLM A:LR,GLM
Heart Sounds	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR

TABLE 12-1. (Continued)

Statistical Analysis for the Cardiovascular Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Overall Electrocardiograph (ECG)	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR L:LR
ECG: Right Bundle Branch Block (RBBB)	PE	D	Abnormal Normal	AGE,RACE PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR,CS,FT A:LR
ECG: Left Bundle Branch Block (LBBB)	PE	D	Abnormal Normal	- -	- -
ECG: Nonspecific ST- and T-Wave Changes	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR
ECG: Bradycardia	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR,FT A:LR,FT

TABLE 12-1. (Continued)

Statistical Analysis for the Cardiovascular Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
ECG: Tachycardia	PE	D	Abnormal Normal	--	--
ECG: Arrhythmia	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR
ECG: Other Diagnoses	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR
Diastolic Blood Pressure (mm Hg)	PE	D/C	Abnormal: >90 Normal: ≤90	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR,GLM A:LR,GLM
Funduscopic Examination	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR,CS,FT A:LR

TABLE 12-1. (Continued)

Statistical Analysis for the Cardiovascular Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Carotid Bruits	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR,CS,FT A:LR
Radial Pulses	PE	D	Abnormal Normal	--	--
Femoral Pulses	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR,CS,FT A:LR
Popliteal Pulses	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR,CS,FT A:LR
Dorsalis Pedis Pulses	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR

TABLE 12-1. (Continued)

Statistical Analysis for the Cardiovascular Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Posterior Tibial Pulses	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR,CS,FT A:LR
Leg Pulses	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR
Peripheral Pulses	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR
All Pulses	PE	D	Abnormal Normal	AGE,RACE, PACKYR, DRKYR, CHOL, %BFAT,PERS, DIFCORT, HRTDIS	U:LR A:LR

TABLE 12-1. (Continued)

Statistical Analysis for the Cardiovascular Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black
Current Cigarette Smoking (CSMOK) (cigarettes/day)	Q-SR	C	--
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	D/C	0 >0-10 >10
Current Alcohol Use (ALC) (drinks/day)	Q-SR	C	--
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	C	--
Cholesterol (CHOL) (mg/dl)	LAB	C	--
High Density Lipoprotein (HDL) (mg/dl)	LAB	C	--
Cholesterol-HDL Ratio (CHOL/HDL)	LAB	C	--
Percent Body Fat (%BFAT)	PE	D/C	Obese: >25% Lean/Normal: ≤25%
Personality Type (PERS)	Q-SR (1985)	D	A direction B direction
Differential Cortisol Response (DIFCORT)	LAB (1985)	D/C	≤0.6 >0.6-4:0 >4.0

TABLE 12-1. (Continued)

Statistical Analysis for the Cardiovascular Examination

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Family History of Heart Disease (HRTDIS)	Q-SR	D	Yes No
Family History of Heart Disease Before Age 50 (HRTDIS50)	Q-SR	D	Yes No

Abbreviations

Data Source:
LAB--1987 SCRF laboratory results
LAB (1985)--1985 SCRF laboratory results
MIL--Air Force military records
PE--1987 SCRF physical exam
Q/PE-SR--Questionnaire and physical examination (self-reported)
Q/PE-V--Questionnaire and physical examination (verified)
Q-SR (1985)--1985 questionnaire (self-reported)
Q-SR--1987 questionnaire (self-reported)

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

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

Statistical Methods:
CS---Chi-square contingency table test
FT--Fisher's exact test
GLM--General linear models analysis
LR--Logistic regression analysis

TABLE 12-2.

Number of Participants Excluded and With Missing Data for the Cardiovascular Assessment

Variable	Variable Use	Assumption (Ranch Hands Only) Minimal	Assumption (Ranch Hands Only) Maximal	Categorized Current Dioxin Ranch Hand	Categorized Current Dioxin Comparison
Verified History of Diabetes or 2-Hour Postprandial Glucose ≥200 mg/dl	EXC	66	82	67	66
Pre-SEA Verified Essential Hypertension or Heart Disease	EXC	10	14	10	20
Pitting and Nonpitting Edema[a,b]	EXC	0	6	6	9
Corticosteroids (1985)[a,c]	EXC	2	2	4	3
Temperature ≥100°F at Laboratory Examination[a,d]	EXC	1	1	1	2
Positive Hepatitis B Surface Antigen[a,d]	EXC	3	4	5	3
Lifetime Alcohol History[a]	COV	6	9	9	2
Personality Type (1985)[a]	COV	13	23	26	34
Differential Cortisol Response (1985)[a]	COV	10	19	21	33
Dorsalis Pedis Pulses[a]	DEP	0	1	1	0
Posterior Tibial Pulses[a]	DEP	0	1	1	0
Leg Pulses[a]	DEP	0	1	1	0
Peripheral Pulses[a]	DEP	0	1	1	0
All Pulses[a]	DEP	0	1	1	0

[a]Participants with a verified history of diabetes, 2-hour postprandial glucose 200 mg/dl or more at 1987 physical examination, or pre-SEA verified essential hypertension or heart disease excluded.

[b]Exclusion from analyses of peripheral pulses only.

[c]Exclusion from analyses adjusted for differential cortisol response.

[d]Exclusion from analyses adjusted for cholesterol.

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

TABLE 12-3.

Analysis of Reported/Verified Essential Hypertension

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	35.5	1.09 (0.93,1.29)	0.300
	Medium	224	37.1		
	High	112	39.3		
b) Maximal (n=647)	Low	173	30.1	1.11 (0.98,1.24)	0.098
	Medium	320	36.6		
	High	154	40.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=440)	1.04 (0.87,1.24)	0.651	DRKYR (p=0.024) %BFAT (p<0.001) HRTDIS (p=0.021)
d) Maximal (n=617)	1.02 (0.90,1.17)**	0.738**	INIT*DIFCORT (p=0.030) RACE (p=0.146) PACKYR (p=0.074) DRKYR (p=0.013) %BFAT (p<0.001) HRTDIS (p<0.001)

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

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
INIT: Log_2 (initial dioxin).

TABLE 12-3. (Continued)

Analysis of Reported/Verified Essential Hypertension

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.288[b]
	≤18.6	32.2 (59)	35.4 (113)	43.5 (46)	1.20 (0.92,1.56)	0.171[c]
	>18.6	34.7 (49)	40.9 (115)	35.9 (64)	1.00 (0.80,1.25)	0.979[c]
f) Maximal (n=647)						0.530[b]
	≤18.6	34.0 (103)	32.9 (167)	39.7 (68)	1.14 (0.95,1.37)	0.153[c]
	>18.6	27.9 (68)	39.6 (154)	39.1 (87)	1.05 (0.89,1.25)	0.532[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=428)			0.202[b]	DRKYR (p=0.018)
	≤18.6	1.20 (0.90,1.60)	0.220[c]	%BFAT (p<0.001)
	>18.6	0.94 (0.74,1.19)	0.600[c]	DIFCORT (p=0.098)
				HRTDIS (p=0.015)
h) Maximal (n=638)			0.506[b]	AGE (p=0.098)
	≤18.6	1.13 (0.92,1.38)	0.260[c]	RACE (p=0.138)
	>18.6	1.03 (0.86,1.24)	0.763[c]	PACKYR (p=0.113)
				DRKYR (p=0.034)
				%BFAT (p<0.001)
				HRTDIS (p=0.001)

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-3. (Continued)

Analysis of Reported/Verified Essential Hypertension

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	32.7	All Categories		0.043
Unknown	320	28.1	Unknown vs. Background	0.80 (0.60,1.08)	0.142
Low	177	37.9	Low vs. Background	1.25 (0.89,1.76)	0.197
High	155	39.4	High vs. Background	1.33 (0.93,1.91)	0.115
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	696	All Categories		0.125**	DXCAT*AGE (p=0.029)
Unknown	315	Unknown vs. Background	0.90 (0.66,1.23)**	0.525**	DRKYR (p=0.068)
Low	173	Low vs. Background	1.26 (0.87,1.82)**	0.218**	CHOL (p<0.001)
High	150	High vs. Background	1.45 (0.98,2.15)**	0.065**	%BFAT (p<0.001)
Total	1,334				HRTDIS (p=0.084)

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.
DXCAT: Categorized current dioxin.

percentages of Ranch Hands in the maximal cohort with essential hypertension were 30.1, 36.6, and 40.3 percent for the low, medium, and high initial dioxin categories.

After adjusting for covariate information, the minimal analysis of essential hypertension remained nonsignificant (Table 12-3 [c]: p=0.651). Based on the maximal assumption, the adjusted analysis detected a significant interaction between initial dioxin and differential cortisol response (Table 12-3 [d]: p=0.030). Appendix Table K-1 presents stratified analyses for each differential cortisol-response stratum.

The stratified analyses displayed a nonsignificant positive association between essential hypertension and initial dioxin for Ranch Hands with a differential cortisol response of 0.6 μg/dl or less (Appendix Table K-1: Adj. RR=1.17, p=0.157) and nonsignificant negative associations for Ranch Hands with higher levels of differential cortisol response (>0.6-4.0 μg/dl: Adj. RR=0.95, p=0.645; >4.0 μg/dl: Adj. RR=0.90, p=0.459).

After deletion of the interaction from the model and adjustment for race, lifetime cigarette smoking history, lifetime alcohol history, percent body fat, differential cortisol, and family history of heart disease, the maximal adjusted analysis of essential hypertension did not detect a significant association with initial dioxin (Table 12-3 [d]: p=0.738).

Results of Analyses Without Adjustment for Percent Body Fat. Further analyses were done excluding percent body fat (and/or cholesterol for subsequent variables) from the model. Percent body fat was significantly associated with initial dioxin. (See Chapter 6 for a discussion of percent body fat treated as a dependent variable or Chapter 10 for a discussion of cholesterol treated as a dependent variable.) Therefore, the association between initial dioxin and essential hypertension in the maximal cohort was evaluated in the context of two models: one with percent body fat and appropriate covariates in the model and the other identical except that it excluded percent body fat. The first model was discussed above; the discussion of the second follows.

The deletion of percent body fat from the model under the maximal assumption caused the interaction between initial dioxin and differential cortisol to become nonsignificant. The results of the model without adjustment for percent body fat concurred with those of the model after the deletion of the initial dioxin-by-differential cortisol response interaction (Appendix Table K-2).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The association between current dioxin and essential hypertension did not differ significantly between time since tour strata based on the minimal and maximal assumptions of the unadjusted and adjusted analyses (Table 12-3 [e-h]: p>0.15 for all analyses).

Results of Analyses Without Adjustment for Percent Body Fat. After percent body fat was removed from the maximal adjusted model, there was a significant positive association between current dioxin and essential hypertension for Ranch Hands with later tours (Appendix Table K-2: Adj. RR=1.25, p=0.023).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis detected a significant overall difference in the incidence of essential hypertension among the four current dioxin categories (Table 12-3 [i]: p=0.043). The relative frequencies of essential hypertension for the background, unknown, low, and high current dioxin categories were 32.7, 28.1, 37.9, and 39.4 percent. The percentages were higher, but not significantly, for Ranch Hands in the low and high categories than for the Comparisons in the background category.

The adjusted analysis of essential hypertension detected a significant interaction between categorized current dioxin and age (Table 12-3 [j]: p=0.029). To examine this interaction, the associations between categorized current dioxin and essential hypertension were analyzed separately for younger and older participants (Appendix Table K-1). For participants born in or after 1942, the incidence of essential hypertension differed significantly among the four current dioxin categories (p=0.021). The percentages of essential hypertension were 24.4, 15.3, 32.9, and 36.9 percent for the background, unknown, low, and high categories. The low versus background and high versus background contrasts were marginally significant with the Ranch Hands having a higher risk of essential hypertension than the Comparisons (low versus background: Adj. RR=1.66, 95% C.I.: [0.94,2.93], p=0.078; high versus background: Adj. RR=1.56, 95% C.I.: [0.95,2.56], p=0.082).

The adjusted analysis of the older participants did not detect any significant differences among the relative frequencies of essential hypertension of the four current dioxin categories (Appendix Table K-1: p=0.989).

After deletion of the categorized current dioxin-by-age interaction from the model and adjusting for age, lifetime alcohol history, cholesterol, percent body fat, and family history of heart disease, the analysis of essential hypertension did not detect a significant overall difference among the four current dioxin categories (Table 12-3 [j]: p=0.125). However, the contrast of the high versus background categories was marginally significant (Adj. RR=1.45, 95% C.I.: [0.99,2.17], p=0.065) with the Ranch Hands having a higher risk of essential hypertension than the Comparisons.

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. After removing cholesterol and percent body fat from the model, the interaction between categorized current dioxin and age was no longer significant (p=0.055). The analysis of the model without adjustment for cholesterol and percent body fat displayed a significant overall contrast of the four current dioxin categories (Appendix Table K-2: p=0.002). The contrast of the Ranch Hands in the unknown category versus the Comparisons in the background category became marginally significant (Adj. RR=0.78, 95% C.I.: [0.58,1.04], p=0.094) with the Ranch Hands having a lower risk of essential hypertension than the Comparisons. In contrast, the increased risk of essential hypertension for Ranch Hands in the high current dioxin category relative to the Comparisons in the background category became significant (Adj. RR=1.70, 95% C.I.: [1.17,2.49], p=0.006).

Reported Heart Disease (Excluding Essential Hypertension)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, the percentage of Ranch Hands who reported having heart disease was not associated significantly with initial dioxin in the minimal cohort (Table 12-4 [a]: p=0.149). However, based on the maximal assumption, there was a significant negative association between initial dioxin and reported heart disease (Table 12-4 [b]: Est. RR=0.85, p=0.007). The percentages of reported heart disease were 45.7, 39.7, and 27.9 percent for the low, medium, and high initial dioxin categories.

After adjusting for covariate information, the minimal analysis detected a significant interaction between initial dioxin and race (Table 12-4 [c]: p=0.017). Stratified analyses displayed a significant negative association between initial dioxin and reported heart disease for the Black stratum (Appendix Table K-1: Adj. RR=0.27, p=0.036) and a nonsignificant association for the non-Black stratum (Adj. RR=0.99, p=0.879). The percentages of Ranch Hands in the Black stratum who reported having heart disease were 70.0, 46.2, and 33.3 percent for the low, medium, and high initial dioxin categories. This interaction may have been affected by the sparse number of Black Ranch Hands in the analysis. Reported heart disease was not associated significantly with initial dioxin after deletion of the interaction with race from the model (Table 12-4 [c]: p=0.505).

After adjusting for age, race, lifetime cigarette smoking history, and family history of heart disease, the negative association between initial dioxin and reported heart disease became marginally significant in the maximal cohort (Table 12-4 [d]: Adj. RR=0.88, p=0.052).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of reported heart disease, the interaction between current dioxin and time since tour was not significant under either the minimal or the maximal assumption (Table 12-4 [e] and [f]: p=0.926 and p=0.779). However, based on the maximal assumption, there was a marginally significant negative association between current dioxin and reported heart disease for Ranch Hands with later tours (Table 12-4 [f]: Est. RR=0.84, p=0.065) and a significant negative association for Ranch Hands with early tours (Est. RR=0.81, p=0.015). The percentages of Ranch Hands who reported having heart disease for the 18.6 years or less time stratum of the maximal cohort decreased as current dioxin increased (low, 43.7%; medium, 35.9%; high, 26.5%). The percentages decreased similarly for the time over 18.6 years stratum (low, 54.4%; medium, 42.2%; high, 27.6%).

The adjustment for age, race, lifetime cigarette smoking history, and family history of heart disease did not change the nonsignificant relationship between current dioxin and time since tour in either the minimal or the maximal cohort (Table 12-4 [g] and [h]: p=0.867 and p=0.670). However, under the maximal assumption, the association between current dioxin and reported heart disease became nonsignificant for Ranch Hands with late tours (Table 12-4 [h]: Adj. RR=0.89, p=0.252) and marginally significant for Ranch Hands with early tours (Adj. RR=0.84, p=0.060).

TABLE 12-4.

Analysis of Reported Heart Disease (Excluding Essential Hypertension)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	42.7	0.88 (0.74,1.05)	0.149
	Medium	224	34.8		
	High	112	29.5		
b) Maximal (n=647)	Low	173	45.7	0.85 (0.75,0.96)	0.007
	Medium	320	39.7		
	High	154	27.9		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	0.94 (0.79,1.13)**	0.505**	INIT*RACE (p=0.017) AGE (p=0.009) PACKYR (p=0.093) HRTDIS (p=0.103)
d) Maximal (n=647)	0.88 (0.78,1.00)	0.052	AGE (p=0.002) RACE (p=0.026) PACKYR (p=0.142) HRTDIS (p=0.075)

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

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-4. (Continued)

Analysis of Reported Heart Disease (Excluding Essential Hypertension)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.926[b]
	≤18.6	40.7 (59)	31.9 (113)	28.3 (46)	0.86 (0.65,1.14)	0.297[c]
	>18.6	46.9 (49)	36.5 (115)	31.3 (64)	0.88 (0.70,1.10)	0.261[c]
f) Maximal (n=647)						0.779[b]
	≤18.6	43.7 (103)	35.9 (167)	26.5 (68)	0.84 (0.69,1.01)	0.065[c]
	>18.6	54.4 (68)	42.2 (154)	27.6 (87)	0.81 (0.68,0.96)	0.015[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=446)			0.867[b]	AGE (p=0.026)
	≤18.6	0.96 (0.72,1.28)	0.788[c]	RACE (p=0.042)
	>18.6	0.93 (0.73,1.18)	0.560[c]	PACKYR (p=0.088) HRTDIS (p=0.083)
h) Maximal (n=647)			0.670[b]	AGE (p=0.006)
	≤18.6	0.89 (0.73,1.08)	0.252[c]	RACE (p=0.030)
	>18.6	0.84 (0.71,1.01)	0.060[c]	PACKYR (p=0.111) HRTDIS (p=0.080)

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-4. (Continued)

Analysis of Reported Heart Disease (Excluding Essential Hypertension)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	38.1	All Categories		0.003
Unknown	320	44.7	Unknown vs. Background	1.31 (1.00,1.71)	0.047
Low	177	37.3	Low vs. Background	0.97 (0.69,1.36)	0.838
High	155	27.1	High vs. Background	0.60 (0.41,0.89)	0.010
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.024	AGE (p<0.001)
Unknown	320	Unknown vs. Background	1.30 (0.99,1.71)	0.055	RACE (p=0.138)
Low	177	Low vs. Background	0.98 (0.70,1.38)	0.916	
High	155	High vs. Background	0.69 (0.47,1.02)	0.062	
Total	1,355				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of reported heart disease differed significantly among the four current dioxin categories in the unadjusted analysis (Table 12-4 [i]: p=0.003). Ranch Hands in the unknown category had a significantly higher incidence of reported heart disease than the Comparisons in the background category (Est. RR=1.31, 95% C.I.: [1.00,1.71], p=0.047). In contrast, the Ranch Hands in the high current dioxin category had a significantly lower incidence of reported heart disease than the Comparisons (Est. RR=0.60, 95% C.I.: [0.41,0.89], p=0.010). The percentages of participants who reported having heart disease were 38.1, 44.7, 37.3, and 27.1 percent for the background, unknown, low, and high current dioxin categories.

After adjusting for age and race, the overall contrast of the four current dioxin categories remained significant (Table 12-4 [j]: p=0.024). However, the contrasts of the unknown versus background category and the high versus background category became only marginally significant (unknown versus background: Adj. RR=1.30, 95% C.I.: [0.99,1.71], p=0.055; high versus background: Adj. RR=0.69, 95% C.I.: [0.47,1.02], p=0.062).

Verified Heart Disease (Excluding Essential Hypertension)

The results of the analyses of verified heart disease were nearly identical to those of the analyses of reported heart disease, since only three of the reported cases of heart disease of the assayed participants were not verified (one Comparison and two Ranch Hands).

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the unadjusted analysis detected a nonsignificant negative association between initial dioxin and verified history of heart disease (excluding essential hypertension) (Table 12-5 [a]: p=0.138). However, based on the maximal assumption, there was a significant negative relationship between initial dioxin and the incidence of verified heart disease (Table 12-5 [b]: Est. RR=0.84, p=0.006). The relative frequencies of verified heart disease decreased steadily for increasing levels of initial dioxin in the maximal cohort (low, 45.7%; medium, 39.7%; high, 27.3%).

The adjusted minimal analysis of verified heart disease (excluding essential hypertension) revealed a significant interaction between initial dioxin and race (Table 12-5 [c]: p=0.014). The stratified analyses displayed a significant negative association between initial dioxin and verified heart disease for the Black stratum (Appendix Table K-1: Adj. RR=0.27, p=0.032) and a nonsignificant negative association for the non-Black stratum (Adj. RR=0.99, p=0.920). The relative frequencies of verified heart disease in both Black and non-Black Ranch Hands decreased with increasing levels of initial dioxin (Black: low, 70%; medium, 46.2%; high, 33.3%; non-Black: low, 40.0%; medium, 33.7%; high, 29.4%).

After deletion of the initial dioxin-by-race interaction from the adjusted minimal model, the negative association between initial dioxin and the incidence of verified heart disease was not significant (Table 12-5 [c]: p=0.532). Similar to unadjusted results, the maximal adjusted analysis of verified heart disease also displayed a significant negative relationship with initial dioxin (Table 12-5 [d]: Adj. RR=0.88, p=0.044).

TABLE 12-5.

Analysis of Verified Heart Disease (Excluding Essential Hypertension)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	42.7	0.88 (0.74,1.04)	0.138
	Medium	224	34.4		
	High	112	29.5		
b) Maximal (n=647)	Low	173	45.7	0.84 (0.75,0.95)	0.006
	Medium	320	39.7		
	High	154	27.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	0.95 (0.79,1.13)**	0.532**	INIT*RACE (p=0.014) AGE (p=0.002) PACKYR (p=0.097)
d) Maximal (n=647)	0.88 (0.78,1.00)	0.044	AGE (p=0.001) RACE (p=0.021)

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

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-5. (Continued)

Analysis of Verified Heart Disease (Excluding Essential Hypertension)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.944[b]
	≤18.6	40.7 (59)	31.9 (113)	28.3 (46)	0.86 (0.65,1.14)	0.297[c]
	>18.6	46.9 (49)	35.7 (115)	31.3 (64)	0.87 (0.69,1.10)	0.250[c]
f) Maximal (n=647)						0.740[b]
	≤18.6	43.7 (103)	35.9 (167)	26.5 (68)	0.84 (0.69,1.01)	0.065[c]
	>18.6	54.4 (68)	42.2 (154)	26.4 (87)	0.80 (0.68,0.95)	0.013[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=446)			0.852[b]	AGE (p=0.019)
	≤18.6	0.97 (0.72,1.29)	0.811[c]	RACE (p=0.038)
	>18.6	0.93 (0.73,1.19)	0.567[c]	PACKYR (p=0.101) HRTDIS (p=0.124)
h) Maximal (n=647)			0.628[b]	AGE (p=0.002)
	≤18.6	0.90 (0.74,1.09)	0.267[c]	RACE (p=0.030)
	>18.6	0.84 (0.70,1.00)	0.056[c]	PACKYR (p=0.120)

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-5. (Continued)

Analysis of Verified Heart Disease (Excluding Essential Hypertension)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	38.0	All Categories		0.002
Unknown	320	44.4	Unknown vs. Background	1.30 (1.00,1.70)	0.053
Low	177	37.3	Low vs. Background	0.97 (0.69,1.36)	0.865
High	155	26.5	High vs. Background	0.59 (0.40,0.87)	0.007
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.021	AGE (p<0.001) RACE (p=0.128)
Unknown	320	Unknown vs. Background	1.29 (0.99,1.70)	0.062	
Low	177	Low vs. Background	0.99 (0.70,1.39)	0.945	
High	155	High vs. Background	0.67 (0.45,1.00)	0.049	
Total	1,355				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Consistent with the initial dioxin analyses, the unadjusted minimal analysis of verified heart disease displayed a nonsignificant interaction between current dioxin and time since tour (Table 12-5 [e]: p=0.944) as well as nonsignificant negative associations with current dioxin within the two time strata. Under the maximal assumption, the associations between current dioxin and the incidence of verified heart disease also did not differ between the time strata (Table 12-5 [f]: p=0.740). However, in the maximal cohort, there was a marginally significant negative association between current dioxin and verified heart disease for Ranch Hands with 18.6 years or less since tour (Adj. RR=0.84, p=0.065) and a significant negative association for Ranch Hands with greater than 18.6 years since tour (Adj. RR=0.80, p=0.013). The relative frequencies of Ranch Hands in the maximal cohort with verified heart disease decreased for increasing levels of current dioxin in both time strata (≤18.6: low, 43.7%; medium, 35.9%; high, 26.5%; >18.6: low, 54.4%; medium, 42.2%; high, 26.4%).

The adjustment for covariate information did not alter the lack of significance of the minimal analysis of the verified incidence of heart disease with current dioxin and time since tour (Table 12-5 [g]: p>0.55 for the interaction and time-specific analyses). After the inclusion of age, race, and lifetime cigarette smoking in the maximal analysis, the interaction between current dioxin and time remained nonsignificant (Table 12-5 [h]: p=0.628). The negative association between current dioxin and verified heart disease became nonsignificant for Ranch Hands with later tours (p=0.267) and marginally significant for Ranch Hands with early tours (Adj. RR=0.84, p=0.056).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the verified incidence of heart disease detected a highly significant difference among the four current dioxin categories (Table 12-5 [i]: p=0.002). Ranch Hands in the unknown current dioxin category had a marginally significant increased risk of verified heart disease over the Comparisons in the background category (Adj. RR=1.30, 95% C.I.: [1.00,1.70], p=0.053), while the Ranch Hands in the high category had a significantly lower risk than the Comparisons in the background category (Adj. RR=0.59, 95% C.I.: [0.40,0.87], p=0.007). The relative frequencies of verified heart disease for the participants in the background, unknown, low, and high current dioxin categories were 38.0, 44.4, 37.3, and 26.5 percent.

After adjusting for age and race in the analysis of verified heart disease, the simultaneous contrast of the four current dioxin categories remained significant (Table 12-5 [j]: p=0.021). Also, similar to the unadjusted analysis, the Ranch Hands in the unknown category had a marginally higher verified incidence of heart disease than the Comparisons in the background category (Adj. RR=1.29, 95% C.I.: [0.99,1.70], p=0.062). The Ranch Hands in the high current dioxin category had a significantly lower incidence of heart disease than the Comparisons in the background current dioxin category (Adj. RR=0.67, 95% C.I.: [0.45,1.00], p=0.049).

Reported/Verified Myocardial Infarction

The frequencies of participants with self-reported and medically verified histories of myocardial infarction were equivalent; therefore, these two endpoints were analyzed as a

single variable: reported/verified myocardial infarction. This variable will be referred to as myocardial infarction.

The primary analyses for myocardial infarction excluded diabetics. However, additional analyses (unadjusted and adjusted for age) were done based on diabetics only. Appendix Table K-4 details the results of these analyses. The results for the initial dioxin analyses and for the current dioxin and time since tour analyses were not significant for diabetics. The unadjusted categorized current dioxin analysis showed a marginally significant increased risk of myocardial infarction for diabetic Ranch Hands in the low current dioxin category relative to diabetic Comparisons in the background category (Est. RR=3.33, 95% C.I.: [0.79,13.81], p=0.097), but this contrast became nonsignificant after adjustment for age (Adj. RR=2.36, 95% C.I.: [0.52,10.52], p=0.263). The incidences of myocardial infarction based on diabetics only were 9.8, 5.3, 26.7, and 6.5 percent for the background, unknown, low, and high current dioxin categories.

The following discussion of the myocardial infarction analyses is based on participants who were not classified as diabetic.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted and adjusted analyses of myocardial infarction did not reveal a significant association with initial dioxin under either the minimal or the maximal assumption (Table 12-6 [a-d]: p>0.15 for all analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The unadjusted analysis of myocardial infarction with current dioxin and time since tour did not exhibit any significant results under either assumption (Table 12-6 [e] and [f]: p>0.30 for each interaction and time-specific analysis).

The adjustment for covariate information did not alter the lack of significance of the current dioxin-by-time since tour interaction in the minimal analysis (Table 12-6 [g]: p=0.705). After adjustment for age, lifetime alcohol history, and cholesterol, the association between current dioxin and the incidence of myocardial infarction did not differ significantly between time strata under the maximal assumption (Table 12-6 [h]: p=0.159). However, for the maximal cohort, there was a marginally significant positive association between current dioxin and myocardial infarction for Ranch Hands with later tours (Table 12-6 [h]: Adj. RR=1.63, p=0.058). The percentages of Ranch Hands with myocardial infarction for this time stratum of the maximal cohort were 1.0, 4.8, and 2.9 percent for low, medium, and high current dioxin.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of myocardial infarction, the overall contrast of the four current dioxin categories was marginally significant (Table 12-6 [i]: p=0.083). The relative frequencies of myocardial infarction for the background, unknown, low, and high categories were 4.6, 2.8, 7.3, and 2.6 percent.

TABLE 12-6.

Analysis of Reported/Verified Myocardial Infarction

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	5.5	0.91 (0.62,1.32)	0.609
	Medium	224	6.3		
	High	112	2.7		
b) Maximal (n=647)	Low	173	2.3	1.13 (0.86,1.48)	0.380
	Medium	320	6.6		
	High	154	2.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=440)	1.05 (0.71,1.55)	0.807	AGE (p<0.001) DRKYR (p=0.041)
d) Maximal (n=634)	1.24 (0.93,1.66)	0.154	AGE (p<0.001) DRKYR (p=0.026) CHOL (p=0.061)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-6. (Continued)

Analysis of Reported/Verified Myocardial Infarction

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)	≤18.6	5.1 (59)	5.3 (113)	2.2 (46)	0.90 (0.48,1.70)	0.862[b] 0.746[c]
	>18.6	6.1 (49)	7.0 (115)	3.1 (64)	0.84 (0.51,1.39)	0.491[c]
f) Maximal (n=647)	≤18.6	1.0 (103)	4.8 (167)	2.9 (68)	1.25 (0.80,1.96)	0.332[b] 0.329[c]
	>18.6	5.9 (68)	7.1 (154)	2.3 (87)	0.94 (0.65,1.35)	0.731[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=440)	≤18.6	1.23 (0.62,2.44)	0.705[b] 0.554[c]	AGE (p<0.001) DRKYR (p=0.038)
	>18.6	1.05 (0.64,1.72)	0.859[c]	
h) Maximal (n=634)	≤18.6	1.63 (0.98,2.69)	0.159[b] 0.058[c]	AGE (p<0.001) DRKYR (p=0.021)
	>18.6	1.04 (0.70,1.53)	0.855[c]	CHOL (p=0.056)

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-6. (Continued)

Analysis of Reported/Verified Myocardial Infarction

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	4.6	All Categories		0.083
Unknown	320	2.8	Unknown vs. Background	0.61 (0.29,1.29)	0.193
Low	177	7.3	Low vs. Background	1.66 (0.85,3.24)	0.135
High	155	2.6	High vs. Background	0.56 (0.19,1.59)	0.274
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	667	All Categories		****	DXCAT*DIFCORT (p=0.005)
Unknown	303	Unknown vs. Background	****	****	AGE (p<0.001)
Low	174	Low vs. Background	****	****	PACKYR (p=0.003)
High	150	High vs. Background	****	****	
Total	1,294				

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

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

The adjusted analysis of myocardial infarction detected a significant interaction between categorized current dioxin and differential cortisol response (Table 12-6 [j]: p=0.005). Appendix Table K-1 presents stratified analyses for each of three specified levels of differential cortisol response. For participants with a differential cortisol response of 0.6 μg/dl or less, the incidence of myocardial infarction differed significantly among the four current dioxin categories (Appendix Table K-1: p<0.001). The percentages of participants with myocardial infarction for the background, unknown, and low current dioxin categories were 3.0, 3.2, and 14.8 percent. There were no myocardial infarctions in the high category; therefore, the relative risk and confidence interval are not given for the high versus background category contrast. The contrast of the Ranch Hands in the low category versus the Comparisons in the background category displayed a significantly higher risk of myocardial infarction for the Ranch Hands (Adj. RR=6.43, 95% C.I.: [2.21,18.68], p=0.001).

The overall categorized current dioxin effect was not significant for participants with a differential cortisol response between 0.6 and 4.0 μg/dl (Appendix Table K-1: p=0.721) or greater than 4.0 μg/dl (p=0.364). The percentages of participants in the moderate differential cortisol-response stratum with myocardial infarction were 4.4, 2.0, 3.2, and 1.6 percent for the background, unknown, low, and high current dioxin categories. In contrast, the corresponding percentages for the high differential cortisol stratum were 7.4, 3.7, 2.0, and 5.9 percent. For the low and moderate strata, the participants in the high category had the lowest incidence of myocardial infarction within their respective strata. However, in the high differential cortisol-response stratum, participants in the high current dioxin category had the highest incidence of myocardial infarction of the Ranch Hands in this stratum.

Physical Examination: Central Cardiac Function Variables

Systolic Blood Pressure (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analyses of systolic blood pressure in continuous form did not detect a significant association with initial dioxin for the minimal and the maximal cohorts (Table 12-7 [a] and [b]: p=0.732 and p=0.220).

The adjusted minimal analysis revealed significant interactions between initial dioxin and age and between initial dioxin and lifetime cigarette smoking history (Table 12-7 [c]: p=0.009 and p=0.024). Appendix Table K-1 presents stratified analyses for each age and lifetime cigarette smoking history combination strata (i.e., born≥1942, 0 pack-years; born≥1942, >0-10 pack-years; etc.).

Only the stratum of younger Ranch Hands who were heavy smokers (>10 pack-years) displayed a significant association between initial dioxin and systolic blood pressure (p=0.014). In this stratum, the adjusted mean systolic blood pressure values became lower as initial dioxin increased (low, 135.59 mm Hg; medium, 130.18 mm Hg; high, 125.84 mm Hg).

For the older Ranch Hands, each of the lifetime cigarette smoking history strata revealed a nonsignificant positive association between initial dioxin and systolic blood pressure in its continuous form (Appendix Table K-1: p>0.10 for all analyses). After

TABLE 12-7.

Analysis of Systolic Blood Pressure (mm Hg) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal (n=446) (R^2<0.001)	Low	110	128.21	0.232 (0.677)	0.732
	Medium	224	127.30		
	High	112	128.64		
b) Maximal (n=647) (R^2=0.002)	Low	173	125.50	0.592 (0.481)	0.220
	Medium	320	127.48		
	High	154	129.05		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c) Minimal (n=443) (R^2=0.087)	Low	110	131.49***	0.144 (0.692)***	0.836***	INIT*AGE (p=0.009) INIT*PACKYR (p=0.024) RACE (p=0.035) CHOL (p=0.010) %BFAT (p<0.001)
	Medium	222	131.22***			
	High	111	132.15***			
d) Maximal (n=643) (R^2=0.087)	Low	172	129.98**	0.376 (0.490)**	0.444**	INIT*PACKYR (p=0.018) AGE (p=0.008) RACE (p=0.013) CHOL (p=0.044) %BFAT (p<0.001)
	Medium	318	130.46**			
	High	153	132.91**			

[a]Slope and standard error based on systolic blood pressure versus log_2 dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

***Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-7. (Continued)

Analysis of Systolic Blood Pressure (mm Hg) (Continuous)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Mean/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[a]	p-Value
e) Minimal (n=446) (R^2=0.002)	≤18.6	128.36 (59)	125.81 (113)	128.43 (46)	0.017 (1.078)	0.961[b] 0.987[c]
	>18.6	127.80 (49)	129.04 (115)	128.55 (64)	0.087 (0.914)	0.924[c]
f) Maximal (n=647) (R^2=0.003)	≤18.6	126.29 (103)	126.75 (167)	126.76 (68)	0.263 (0.731)	0.781[b] 0.719[c]
	>18.6	125.56 (68)	128.17 (154)	129.93 (87)	0.540 (0.679)	0.427[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
g) Minimal (n=431) (R^2=0.084)	≤18.6	130.40** (56)	129.11** (109)	134.68** (42)	-0.318 (1.106)**	0.935**[b] 0.774**[c]	CURR*TIME*HRTDIS (p=0.048)
	>18.6	131.94** (48)	132.77** (113)	131.13** (63)	-0.433 (0.902)**	0.632**[c]	RACE (p=0.078) CHOL (p=0.009) %BFAT (p<0.001) PERS (p=0.105)
h) Maximal (n=643) (R^2=0.088)	≤18.6	131.00** (102)	130.31** (165)	131.18** (67)	0.173 (0.744)**	0.727**[b] 0.816**[c]	CURR*TIME*AGE (p=0.019)
	>18.6	128.70** (68)	130.68** (154)	132.62** (87)	0.512 (0.680)**	0.452**[c]	RACE (p=0.012) PACKYR (p=0.063) CHOL (p=0.064) %BFAT (p<0.001)

[a]Slope and standard error based on systolic blood pressure versus log_2 dioxin.

[b]Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

[c]Test of significance for slope equal to 0 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
CURR: Log_2 (current dioxin).
TIME: Time since tour.

TABLE 12-7. (Continued)

Analysis of Systolic Blood Pressure (mm Hg) (Continuous)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Mean	Contrast	Difference of Means (95% C.I.)	p-Value
Background	703	126.65	All Categories		0.247
Unknown	320	125.17	Unknown vs. Background	-1.48 (-3.77,0.81)	0.205
Low	177	126.79	Low vs. Background	0.13 (-2.72,2.98)	0.927
High	155	128.54	High vs. Background	1.89 (-1.12,4.90)	0.218
Total	1,355		(R^2=0.003)		

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	662	128.43***	All Categories		0.491***	DXCAT*AGE (p=0.006)
Unknown	301	127.81***	Unknown vs. Background	-0.62 (-2.90,1.65)***	0.592***	RACE (p=0.143)
Low	173	128.44***	Low vs. Background	0.01 (-2.76,2.78)***	0.996***	CHOL (p=0.023)
High	149	130.46***	High vs. Background	2.02 (-1.00,5.04)***	0.189***	%BFAT (p<0.001)
Total	1,285		(R^2=0.120)			DIFCORT (p=0.010)
						HRTDIS (p=0.124)

***Categorized current dioxin-by-covariate interaction ($p \leq 0.01$); adjusted mean, confidence interval, and p-value derived from a model after deletion of the interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

deletion of the two interactions from the model, the minimal adjusted analysis was nonsignificant (Table 12-7 [c]: p=0.836).

Under the maximal assumption, the adjusted analysis detected a significant interaction between initial dioxin and lifetime cigarette smoking history (Table 12-7 [d]: p=0.018). In order to examine this interaction, separate analyses were performed for each lifetime cigarette smoking history category (Appendix Table K-1). For Ranch Hands who were nonsmokers, there was a marginally significant positive association between initial dioxin and systolic blood pressure (p=0.079). The adjusted mean systolic blood pressure values for this stratum increased with increasing initial dioxin (low, 129.91 mm Hg; medium, 130.50 mm Hg; high, 134.92 mm Hg). The analysis of Ranch Hands who were smokers with 10 or fewer pack-years displayed a nonsignificant positive association (p=0.278). In contrast, Ranch Hands with more than 10 pack-years had a nonsignificant negative association between initial dioxin and systolic blood pressure (p=0.308).

After excluding the interaction from the model, the maximal analysis displayed a nonsignificant positive association between initial dioxin and systolic blood pressure in its continuous form (Table 12-7 [d]: p=0.444).

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. After exclusion of cholesterol and percent body fat from the model, the minimal adjusted analysis still detected significant interactions between initial dioxin and age and between initial dioxin and lifetime cigarette smoking history (Appendix Table K-2: p=0.033 and p=0.031, respectively). In the stratified analyses, the negative association between initial dioxin and systolic blood pressure became only marginally significant for the younger Ranch Hands who were heavy smokers (Appendix Table K-3: p=0.081). The adjusted mean systolic blood pressures for Ranch Hands in this stratum were 131.69, 127.01, and 125.24 mm Hg for the low, medium, and high initial dioxin categories.

In contrast, the positive association between initial dioxin and systolic blood pressure in its continuous form increased in significance for the older Ranch Hands who were moderate smokers (p=0.094). The adjusted mean systolic blood pressures for these Ranch Hands were 129.65, 126.48, and 140.33 mm Hg for the low, medium, and high initial dioxin categories.

Under the maximal assumption, after the exclusion of cholesterol and percent body fat from the model, the adjusted analysis of systolic blood pressure in its continuous form continued to detect a significant interaction between initial dioxin and lifetime cigarette smoking history (Appendix Table K-2: p=0.013). In the stratified analyses without adjustment for cholesterol and percent body fat, the positive association between initial dioxin and systolic blood pressure became significant for nonsmokers (Appendix Table K-3: p=0.007) and marginally significant for moderate smokers (p=0.099). For Ranch Hands with zero pack-years, the adjusted mean systolic blood pressures were 128.04, 129.87, and 135.50 mm Hg for the low, medium, and high initial dioxin categories. Similarly, for Ranch Hands with 10 or fewer pack-years, the adjusted mean systolic blood pressures were 123.12, 127.05, and 132.78 mm Hg for the low, medium, and high initial dioxin categories.

After further deletion of the initial dioxin-by-lifetime cigarette smoking history interaction, the maximal analysis displayed a significant positive association between initial dioxin and systolic blood pressure in its continuous form (Appendix Table K-2: p=0.049). The adjusted mean systolic blood pressure increased steadily with increasing levels of initial dioxin (low, 128.31 mm Hg; medium, 129.73 mm Hg; high, 133.12 mm Hg).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of systolic blood pressure in its continuous form, the interaction between current dioxin and time since tour was not significant under the minimal and maximal assumptions (Table 12-7 [e] and [f]: p=0.961 and p=0.781).

The adjusted minimal analysis detected a significant interaction among current dioxin, time since tour, and family history of heart disease (Table 12-7 [g]: p=0.048). Appendix Table K-1 presents stratified analyses performed to investigate this interaction. For Ranch Hands with a history of heart disease in their family, the interaction between current dioxin and time was marginally significant (p=0.072). There was a positive association between current dioxin and systolic blood pressure for Ranch Hands with later tours and a negative association for Ranch Hands with earlier tours. However, both of these associations were nonsignificant (p=0.146 and p=0.286, respectively).

In contrast, the minimal analysis of Ranch Hands without a family history of heart disease displayed nonsignificant negative associations between current dioxin and systolic blood pressure for both time strata. These associations also did not differ significantly between the time strata (p>0.25 for the interaction and time-specific analyses).

After deletion of the interaction from the model, the minimal adjusted analysis of systolic blood pressure in its continuous form also revealed nonsignificant results (Table 12-7 [g]: p>0.60 for the interaction and time-specific analyses).

Under the maximal assumption, the adjusted analysis of systolic blood pressure revealed a significant interaction among current dioxin, time since tour, and age (Table 12-7 [h]: p=0.019). Appendix Table K-1 presents separate analyses for younger and older Ranch Hands to examine this interaction. No significant results were found in the analysis of the younger Ranch Hands. However, for the older Ranch Hands, the association between current dioxin and systolic blood pressure differed significantly between the two time strata (p=0.030). For the younger Ranch Hands, the association between current dioxin and systolic blood pressure was positive for those with later tours and negative for those with early tours. Each of these associations within the time strata was nonsignificant (p>0.25 for all analyses). In contrast, the direction of the associations was opposite within the time strata for the older Ranch Hands: negative for Ranch Hands with late tours (p=0.171) and positive for Ranch Hands with early tours (p=0.075). The adjusted mean systolic blood pressure values for the older Ranch Hands with early tours were 130.41, 129.97, and 136.38 mm Hg for low, medium, and high current dioxin.

After excluding the current dioxin-by-time-by-age interaction from the model, the results of the adjusted maximal analyses revealed a lack of significance as did the unadjusted maximal analyses (Table 12-7 [h]: p>0.45 for the interaction and time-specific analyses).

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. After excluding cholesterol and percent body fat from the adjusted minimal model, the analysis of systolic blood pressure in its continuous form no longer displayed a significant interaction among current dioxin, time since tour, and family history of heart disease. Similarly, the adjusted maximal analysis excluding cholesterol and percent body fat did not exhibit a significant interaction among current dioxin, time, and age.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of systolic blood pressure in its continuous form did not detect any significant differences among the four current dioxin categories (Table 12-7 [i]: $p>0.20$ for each contrast).

The adjusted analysis of systolic blood pressure in its continuous form revealed a significant interaction between categorized current dioxin and age (Table 12-7 [j]: $p=0.006$). Appendix Table K-1 presents stratified analyses for younger and older participants in order to examine this interaction. For the younger participants, the overall contrast of the four current dioxin categories was not significant ($p=0.278$). However, the specific contrast of the Ranch Hands in the low category versus the Comparisons in the background category was marginally significant ($p=0.051$) with the Ranch Hands having a higher mean systolic blood pressure than the Comparisons. The adjusted mean systolic blood pressures for the younger participants were 125.11, 125.70, 129.34, and 125.98 mm Hg for the background, unknown, low, and high current dioxin categories.

For the older participants, the overall contrast of the four current dioxin categories was marginally significant (Appendix Table K-1: $p=0.076$). The contrast of the Ranch Hands in the low category versus the Comparisons in the background category was also marginally significant ($p=0.054$) with the Ranch Hands having a lower adjusted mean systolic blood pressure than the Comparisons in the background current dioxin category. The adjusted mean systolic blood pressures were 130.76, 129.23, 127.14, and 133.98 mm Hg for the background, unknown, low, and high current dioxin categories.

After deletion of the categorized current dioxin-by-age interaction from the model, the adjusted analysis of systolic blood pressure in its continuous form displayed nonsignificant results concurrent with those of the unadjusted analysis (Table 12-7 [j]: $p>0.15$ for each contrast).

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. After the deletion of cholesterol and percent body fat from the adjusted model of systolic blood pressure in its continuous form, the interaction between categorized current dioxin and age remained significant (Appendix Table K-2: $p=0.022$). The stratified analyses of systolic blood pressure in its continuous form performed without cholesterol and percent body fat in the model showed little change in the analyses of the younger participants. However, for the older participants, the overall contrast of the four current dioxin categories became significant (Appendix Table K-3: $p=0.019$). Also, the contrasts of the Ranch Hands in the unknown and high categories versus the Comparisons in the background category increased in significance ($p=0.060$ and $p=0.071$, respectively), while the contrast of the Ranch Hands in the low category versus the Comparisons in the background category became nonsignificant

(p=0.146). The adjusted mean systolic blood pressures for the older Ranch Hands were 131.51, 128.68, 128.70, and 136.22 mm Hg for the background, unknown, low, and high current dioxin categories.

Systolic Blood Pressure (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The association between initial dioxin and discretized systolic blood pressure was not significant in the unadjusted analysis under the minimal and the maximal assumptions (Table 12-8 [a] and [b]: p=0.849 and p=0.330).

The minimal adjusted analysis revealed a significant interaction between initial dioxin and personality type (Table 12-8 [c]: p=0.036). Stratifying by personality type, there was a significant negative association between initial dioxin and discretized systolic blood pressure for type A Ranch Hands (Appendix Table K-1: Adj. RR=0.70, p=0.050). The relative frequencies of type A Ranch Hands with abnormally high systolic blood pressure were 26.9, 17.9, and 11.4 percent for the low, medium, and high initial dioxin categories. For type B Ranch Hands, there was a nonsignificant positive relationship between initial dioxin and the prevalence of abnormally high systolic blood pressure (p=0.447).

The adjusted analysis of the minimal cohort excluding the initial dioxin-by-personality type interaction from the model displayed nonsignificant results consistent with those of the unadjusted minimal analysis (Table 12-8 [c]: p=0.503). Under the maximal assumption, the adjusted analysis did not detect a significant relationship between initial dioxin and discretized systolic blood pressure (Table 12-8 [d]: p=0.524).

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. The minimal adjusted analysis of discretized systolic blood pressure without cholesterol and percent body fat in the model also revealed a significant interaction between initial dioxin and personality type (Appendix Table K-2: p=0.043). Stratified analyses displayed a marginally significant negative association between initial dioxin and systolic blood pressure for type A Ranch Hands (Appendix Table K-3: Adj. RR=0.73, p=0.087).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under both the minimal and the maximal assumptions, the current dioxin-by-time since tour interactions were not significant in the unadjusted analysis of discretized systolic blood pressure (Table 12-8 [e] and [f]: p=0.675 and p=0.647, respectively).

Under the minimal assumption, the adjusted analysis of the prevalence of abnormally high systolic blood pressure revealed a significant interaction among current dioxin, time since tour, and personality type (Table 12-8 [g]: p=0.006). To examine this interaction, stratified analyses were performed for both personality type strata (Appendix Table K-1). For type A Ranch Hands, the interaction between current dioxin and time since tour was marginally significant (p=0.076). There was a significant negative association between current dioxin and systolic blood pressure for type A Ranch Hands with late tours (Adj. RR=0.41, p=0.017). The percentages of abnormally high systolic blood pressure for these Ranch Hands were 32.3, 20.5, and 5.6 percent for low, medium, and high current dioxin. There

TABLE 12-8.

Analysis of Systolic Blood Pressure (Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	22.7	0.98 (0.80,1.20)	0.849
	Medium	224	19.2		
	High	112	21.4		
b) Maximal (n=647)	Low	173	13.9	1.07 (0.93,1.24)	0.330
	Medium	320	20.6		
	High	154	22.1		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=431)	0.93 (0.76,1.15)**	0.503**	INIT*PERS (p=0.036) RACE (p=0.042) CHOL (p=0.027) %BFAT (p<0.001)
d) Maximal (n=643)	1.05 (0.90,1.23)	0.524	AGE (p=0.047) RACE (p=0.005) CHOL (p=0.007) %BFAT (p<0.001)

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

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-8. (Continued)

Analysis of Systolic Blood Pressure (Discrete)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.675[b]
(n=446)	≤18.6	22.0 (59)	15.0 (113)	23.9 (46)	1.00 (0.72,1.38)	0.997[c]
	>18.6	24.5 (49)	22.6 (115)	20.3 (64)	0.91 (0.70,1.19)	0.505[c]
f) Maximal						0.647[b]
(n=647)	≤18.6	15.5 (103)	16.8 (167)	20.6 (68)	1.08 (0.86,1.35)	0.528[c]
	>18.6	16.2 (68)	23.4 (154)	21.8 (87)	1.00 (0.82,1.22)	0.979[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			****	CURR*TIME*PERS
(n=431)	≤18.6	****	****	(p=0.006)
	>18.6	****	****	RACE (p=0.051)
				CHOL (p=0.045)
				%BFAT (p=0.001)
h) Maximal			0.670**[b]	CURR*TIME*PERS
(n=621)	≤18.6	1.00 (0.78,1.29)**	0.978**[c]	(p=0.047)
	>18.6	0.94 (0.76,1.15)**	0.527**[c]	RACE (p=0.017)
				CHOL (p=0.006)
				%BFAT (p<0.001)
				HRTDIS (p=0.134)

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

****Log_2 (current dioxin)-by-time-by-covariate interaction ($p\leq0.01$); adjusted relative risk, confidence interval, and p-value not presented.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-8. (Continued)

Analysis of Systolic Blood Pressure (Discrete)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	19.6	All Categories		0.560
Unknown	320	16.6	Unknown vs. Background	0.81 (0.57,1.15)	0.244
Low	177	18.1	Low vs. Background	0.90 (0.59,1.38)	0.640
High	155	21.3	High vs. Background	1.11 (0.72,1.70)	0.640
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	661	All Categories		****	DXCAT*AGE (p<0.001)
Unknown	300	Unknown vs. Background	****	****	DXCAT*DIFCORT (p=0.036)
Low	172	Low vs. Background	****	****	RACE (p=0.110)
High	147	High vs. Background	****	****	PACKYR (p=0.102)
Total	1,280				CHOL (p=0.010)
					%BFAT (p<0.001)
					PERS (p=0.087)
					HRTDIS (p=0.066)

****Categorized current dioxin-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

was also a nonsignificant negative association between current dioxin and the prevalence of abnormally high systolic blood pressure for type A Ranch Hands with early tours (Adj. RR=0.86, p=0.542).

For type B Ranch Hands, the stratified analysis revealed a significant current dioxin-by-time since tour interaction (Appendix Table K-1: p=0.024). Type B Ranch Hands with later tours had a significant increased risk of abnormally high systolic blood pressure (Adj. RR=1.57, p=0.047), while the analysis of type B Ranch Hands with earlier tours displayed a nonsignificant negative association between current dioxin and systolic blood pressure (Adj. RR=0.83, p=0.298).

The maximal adjusted analysis of discretized systolic blood pressure also revealed a significant interaction among current dioxin, time since tour, and personality type (Table 12-8 [h]: p=0.047). Stratified analyses detected a nonsignificant current dioxin-by-time interaction for type A Ranch Hands (Appendix Table K-1: p=0.228) and a marginally significant interaction for type B Ranch Hands (p=0.078). For type A Ranch Hands, there were nonsignificant negative associations between discretized systolic blood pressure and current dioxin for both time strata (≤18.6: Adj. RR=0.71, p=0.106; >18.6: Adj. RR=0.97, p=0.851). Type B Ranch Hands with later tours had a marginally significant increased risk of abnormally high systolic blood pressure (Adj. RR=1.33, p=0.094). However, type B Ranch Hands with early tours had a nonsignificant decreased risk (Adj. RR=0.91, p=0.486).

After deletion of the current dioxin-by-time-by-personality type from the maximal adjusted model, there were no significant results linking current dioxin, time since tour, and the prevalence of abnormally high systolic blood pressure (Table 12-8 [h]: p>0.50 for each analysis).

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. Under the maximal assumption, the adjusted analysis of discretized systolic blood pressure without cholesterol and percent body fat in the model also displayed a significant interaction among current dioxin, time since tour, and personality type (Appendix Table K-2: p=0.040). The stratified analyses showed the positive association between current dioxin and systolic blood pressure changed from marginally significant to significant for type B Ranch Hands with late tours (Adj. RR=1.42, p=0.031). The current dioxin-by-time interaction also became significant (p=0.095).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of discretized systolic blood pressure did not detect any significant differences among the four current dioxin categories (Table 12-8 [i]: p>0.20 for each contrast).

The adjusted analysis of discretized systolic blood pressure revealed significant interactions between categorized current dioxin and age and between categorized current dioxin and differential cortisol response (Table 12-8 [j]: p<0.001 and p=0.036, respectively). In order to explore these interactions, separate analyses were conducted for younger and older participants (Appendix Table K-1). In the analysis of younger participants, the interaction between categorized current dioxin and differential cortisol was not significant.

For these younger participants, the overall contrast of the four current dioxin categories was not significant (p=0.144). However, the percentage of Ranch Hands in the low category with abnormally high systolic blood pressure was significantly higher than the corresponding percentage of Comparisons in the background category (Adj. RR=2.30, 95% C.I.: [1.15,4.59], p=0.018). The relative frequencies of participants with abnormally high systolic blood pressure were 11.8, 9.5, 21.6, and 17.0 percent for the background, unknown, low, and high current dioxin categories.

In the analysis of the older participants, the interaction between categorized current dioxin and differential cortisol response was significant; thus, Appendix Table K-1 presents stratified results for each differential cortisol-response stratum for the older participants. There were no significant results for older participants with a differential cortisol response of 0.6 μg/dl or less (p>0.65 for each contrast). The relative frequencies of abnormally high systolic blood pressure for the background, unknown, low, and high current dioxin categories for this stratum were 25.7, 25.0, 29.0, and 21.4 percent.

The analysis of the older participants with a differential cortisol response greater than 0.6 μg/dl but less than 4.0 μg/dl detected a significant difference in the prevalence of abnormally high systolic blood pressure among the four current dioxin categories (Appendix Table K-1: p=0.016). Specifically, the percentage of Ranch Hands with high systolic blood pressure in the unknown category was significantly lower than the corresponding percentage of Comparisons in the background category (Adj. RR=0.29, 95% C.I.: [0.10,0.79], p=0.016). Similarly, the Ranch Hands in the low category had a marginally lower percentage of abnormally high systolic blood pressure than the Comparisons in the background category (Adj. RR=0.40, 95% C.I.: [0.15,1.07], p=0.068). For this stratum, the relative frequencies of abnormally high systolic blood pressure for the background, unknown, low, and high current dioxin categories were 27.2, 8.1, 15.0, and 31.6 percent.

For the stratum of older participants with a differential cortisol response greater than 4.0 μg/dl, the analysis detected a significant difference in the prevalence of abnormally high systolic blood pressure values among the four current dioxin categories (Appendix Table K-1: p=0.007). The Ranch Hands in the low category had a significantly lower risk of high systolic blood pressure than the Comparisons in the background category (Adj. RR=0.08, 95% C.I.: [0.01,0.66], p=0.019). The relative frequencies of participants with abnormally high systolic blood pressure were 26.6, 27.5, 3.7 and 35.7 percent for the background, unknown, low, and high current dioxin categories.

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. The adjusted analysis of discretized systolic blood pressure excluding cholesterol and percent body fat from the model detected a significant interaction between categorized current dioxin and age (Appendix Table K-2: p=0.002). In the analysis of the younger participants, the Ranch Hands in the low current dioxin category had a significantly higher risk of abnormally high systolic blood pressure than the Comparisons in the background category (Appendix Table K-3: Adj. RR=2.01, 95% C.I.: [1.04,3.91], p=0.038).

For the older participants, there was a marginally significant difference among the percentages of participants with abnormally high systolic blood pressure for the four current

dioxin categories (Appendix Table K-3: p=0.095). The Ranch Hands in the low category had a significantly lower risk of high systolic blood pressure than the Comparisons in the background category (Adj. RR=0.53, 95% C.I.: [0.30,0.96], p=0.037). The older participants had a notably higher percentage of abnormal systolic blood pressure than younger participants in the corresponding categories, with the exception of the low category (born≥1942: background, 11.8%; unknown, 9.5%; low, 21.3%; high, 17.0%; born<1942: background, 26.5%; unknown, 20.4%; low, 16.3%; high, 29.2%).

Heart Sounds

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted and adjusted analyses revealed nonsignificant associations between initial dioxin and heart sounds under the minimal and maximal assumptions (Table 12-9 [a-d]: p>0.65 for all analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The associations between heart sounds and current dioxin did not differ between time since tour strata in the unadjusted minimal and maximal analyses (Table 12-9 [e] and [f]: p=0.688 and p=0.159).

The adjusted analysis of heart sounds detected significant interactions among current dioxin, time since tour, and lifetime cigarette smoking history and among current dioxin, time since tour, and family history of heart disease for both the minimal (Table 12-9 [g]: p=0.007 and p=0.001, respectively) and maximal cohorts (Table 12-9 [h]: p=0.014 and p=0.006, respectively). Based on the minimal assumption, the interaction among current dioxin, time, and lifetime cigarette smoking history was not significant for Ranch Hands with a family history of heart disease. However, the analysis of these Ranch Hands revealed a marginally significant positive association between current dioxin and heart sounds for Ranch Hands with early tours (Appendix Table K-1: Adj. RR=2.66, p=0.070). Within the greater than 18.6 years time stratum, the relative frequencies of Ranch Hands with abnormal heart sounds were 12.0 and 6.3 percent for medium and high current dioxin. No Ranch Hands in this stratum with low current dioxin had an abnormal heart sound.

In the stratified analysis of Ranch Hands without a family history of heart disease in the minimal cohort, the interaction among current dioxin, time since tour, and lifetime cigarette smoking history was significant. For nonsmokers, there was a significant current dioxin-by-time interaction (p=0.014) and a nonsignificant negative association between current dioxin and heart sounds for Ranch Hands with later tours (p=0.467); for moderate smokers, there was a nonsignificant positive association for Ranch Hands with later tours (p=0.319); and for heavy smokers, there was a nonsignificant positive association for Ranch Hands with early tours (p=0.520). For both nonsmokers and moderate smokers with early tours and heavy smokers with late tours, there were no Ranch Hands with abnormal heart sounds for medium and high current dioxin.

Under the maximal assumption, the interaction among current dioxin, time since tour, and lifetime cigarette smoking history was only significant for Ranch Hands without a family history of heart disease. For Ranch Hands with a history of heart disease in their family, the

TABLE 12-9.

Analysis of Heart Sounds

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	6.4	0.93 (0.62,1.40)	0.726
	Medium	224	3.6		
	High	112	3.6		
b) Maximal (n=647)	Low	173	4.6	0.98 (0.73,1.31)	0.875
	Medium	320	3.8		
	High	154	3.9		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=440)	1.03 (0.68,1.57)	0.876	AGE (p=0.016) DRKYR (p=0.109)
d) Maximal (n=647)	1.07 (0.79,1.46)	0.654	AGE (p=0.004) HRTDIS (p=0.079)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-9. (Continued)

Analysis of Heart Sounds

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.688[b]
	≤18.6	6.8 (59)	0.9 (113)	4.4 (46)	0.76 (0.34,1.73)	0.515[c]
	>18.6	10.2 (49)	4.4 (115)	3.1 (64)	0.93 (0.56,1.53)	0.761[c]
f) Maximal (n=647)						0.159[b]
	≤18.6	5.8 (103)	3.0 (167)	2.9 (68)	0.73 (0.43,1.24)	0.249[c]
	>18.6	1.5 (68)	5.2 (154)	4.6 (87)	1.16 (0.79,1.69)	0.456[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=440)			****	CURR*TIME*PACKYR (p=0.007)
	≤18.6	****	****	CURR*TIME*HRTDIS (p=0.001)
	>18.6	****	****	AGE (p=0.036)
				DRKYR (p=0.034)
h) Maximal (n=647)			****	CURR*TIME*PACKYR (p=0.014)
	≤18.6	****	****	CURR*TIME*HRTDIS (p=0.006)
	>18.6	****	****	AGE (p=0.007)

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
****Log_2 (current dioxin)-by-time-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-9. (Continued)

Analysis of Heart Sounds

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	4.3	All Categories		0.547
Unknown	320	3.1	Unknown vs. Background	0.72 (0.35,1.50)	0.384
Low	177	2.3	Low vs. Background	0.52 (0.18,1.49)	0.223
High	155	3.9	High vs. Background	0.90 (0.37,2.21)	0.824
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.438	AGE (p=0.004) PACKYR (p=0.082) HRTDIS (p=0.041)
Unknown	320	Unknown vs. Background	0.69 (0.33,1.44)	0.325	
Low	177	Low vs. Background	0.53 (0.18,1.52)	0.237	
High	155	High vs. Background	1.19 (0.48,3.00)	0.707	
Total	1,355				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

associations between current dioxin and heart sounds were significantly different between the time strata (Appendix Table K-1: p=0.002). The analyses detected a marginally significant negative association between current dioxin and abnormal heart sounds for Ranch Hands with later tours (Adj. RR=0.21, p=0.059) and a marginally significant positive association for Ranch Hands with early tours (Adj. RR=1.90, p=0.065).

For Ranch Hands without a family history of heart disease, the interaction among current dioxin, time since tour, and lifetime cigarette history was significant. In the analysis of Ranch Hands who were nonsmokers and heavy smokers, there were no significant results. However, the analysis of moderate smokers detected a marginally significant positive association between current dioxin and abnormal heart sounds for Ranch Hands with later tours (Appendix Table K-1: Adj. RR=3.11, p=0.071).

Abnormal heart sounds were rare in Ranch Hands; thus, the above interactions may have been caused or affected by the sparse number of abnormalities in the analyses.

Model 3: Ranch Hand and Comparisons by Current Dioxin Category

The prevalence of abnormal heart sounds was not significantly different among the four current dioxin categories in the unadjusted and adjusted analyses (Table 12-9 [i] and [j]: p=0.547 and p=0.438). However, relatively more Comparisons with abnormal heart sounds were found in the background category than Ranch Hands with abnormal heart sounds in any of the three other categories (4.3%, 3.1%, 2.3%, and 3.9% for the background, unknown, low, and high current dioxin categories).

Overall Electrocardiograph (ECG)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The prevalence of an abnormal overall ECG was not significantly associated with initial dioxin for either the unadjusted minimal or maximal analysis (Table 12-10 [a] and [b]: p=0.443 and p=0.712). These findings did not change after covariate adjustment (Table 12-10 [c] and [d]: p=0.671 and p=0.460 for the minimal and maximal analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of the overall ECG findings, under both minimal and maximal assumptions, the interactions between current dioxin and time since tour were not significant (Table 12-10 [e] and [f]: p=0.213 and p=0.375). The associations between current dioxin and the overall ECG findings were also nonsignificant within the time strata of both minimal and maximal cohorts.

After adjusting for age and race in both the minimal and maximal analyses of the overall ECG findings, the interactions between current dioxin and time since tour remained nonsignificant (Table 12-10 [g] and [h]: p=0.105 and p=0.249). However, for Ranch Hands with 18.6 years or less since tour in the minimal cohort, there was a marginally significant positive association between current dioxin and the overall ECG findings (Table 12-10 [g]: Adj. RR=1.39, p=0.085). The percentages of Ranch Hands in this stratum with abnormal ECG findings were 13.6, 15.9, and 13.0 percent for low, medium, and high current dioxin.

TABLE 12-10.

Analysis of Overall Electrocardiograph (ECG)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	16.4	0.92 (0.74,1.15)	0.443
	Medium	224	18.3		
	High	112	13.4		
b) Maximal (n=647)	Low	173	16.2	0.97 (0.83,1.14)	0.712
	Medium	320	17.5		
	High	154	13.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	1.05 (0.83,1.33)	0.671	AGE (p<0.001) RACE (p=0.110) %BFAT (p=0.136)
d) Maximal (n=647)	1.07 (0.90,1.26)	0.460	AGE (p<0.001) RACE (p=0.093)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-10. (Continued)

Analysis of Overall Electrocardiograph (ECG)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.213[b]
	≤18.6	13.6 (59)	15.9 (113)	13.0 (46)	1.06 (0.74,1.50)	0.764[c]
	>18.6	22.5 (49)	18.3 (115)	15.6 (64)	0.78 (0.58,1.06)	0.117[c]
f) Maximal (n=647)						0.375[b]
	≤18.6	15.5 (103)	14.4 (167)	13.2 (68)	1.03 (0.81,1.31)	0.821[c]
	>18.6	19.1 (68)	19.5 (154)	14.9 (87)	0.89 (0.71,1.10)	0.281[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=446)			0.105[b]	AGE (p<0.001)
	≤18.6	1.39 (0.95,2.03)	0.085[c]	RACE (p=0.117)
	>18.6	0.94 (0.69,1.28)	0.688[c]	
h) Maximal (n=647)			0.249[b]	AGE (p<0.001)
	≤18.6	1.21 (0.93,1.58)	0.152[c]	RACE (p=0.086)
	>18.6	0.99 (0.79,1.25)	0.936[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-10. (Continued)

Analysis of Overall Electrocardiograph (ECG)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	18.5	All Categories		0.288
Unknown	320	14.4	Unknown vs. Background	0.74 (0.51,1.07)	0.107
Low	177	18.1	Low vs. Background	0.97 (0.63,1.49)	0.899
High	155	14.2	High vs. Background	0.73 (0.45,1.19)	0.206
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.342	AGE (p<0.001)
Unknown	320	Unknown vs. Background	0.72 (0.50,1.05)	0.090	RACE (p=0.049)
Low	177	Low vs. Background	1.01 (0.65,1.57)	0.948	PACKYR (p=0.133)
High	155	High vs. Background	1.01 (0.61,1.67)	0.978	
Total	1,355				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the overall ECG findings did not detect any significant differences among the four current dioxin categories (Table 12-10 [i]: p>0.10 for all contrasts).

The adjustment for age, race, and lifetime cigarette smoking history did not change the lack of significance of the simultaneous contrast of the four current dioxin categories (Table 12-10 [j]: p=0.342). However, the Ranch Hands in the unknown category had a marginally lower risk of abnormal ECG results than the Comparisons in the background category (Adj. RR=0.72, 95% C.I.: [0.50,1.05], p=0.090). The relative frequencies of abnormal ECG findings were 18.5, 14.4, 18.1, and 14.2 percent for the background, unknown, low, and high current dioxin categories.

ECG: Right Bundle Branch Block (RBBB)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, the association between RBBB and initial dioxin was not significant for either the minimal or the maximal cohort (Table 12-11 [a] and [b]: p=0.737 and p=0.985, respectively). Adjusted analyses were not performed due to the sparse number of abnormalities.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal assumption, only two Ranch Hands were diagnosed with RBBB (>18.6 years since tour, medium current dioxin). The association between current dioxin and RBBB was nonsignificant (p=0.996). In the maximal unadjusted analysis, there were three Ranch Hands diagnosed with RBBB. In the 18.6 years or less time stratum of the maximal cohort, only one Ranch Hand had RBBB; he was in the low current dioxin category. Thus, relative risks, confidence intervals, and p-values were not presented for this stratum. In the time greater than 18.6 years stratum, there was a nonsignificant positive association between current dioxin and RBBB (Table 12-11 [d]: p=0.595). Similar to the initial dioxin analyses, adjusted models were not investigated in the current dioxin and time analyses due to the sparse number of abnormalities.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

Neither the unadjusted nor the adjusted analysis detected a significant difference in the prevalence of RBBB among the four current dioxin categories (Table 12-11 [e] and [f]: p=0.467 and p=0.649).

ECG: Left Bundle Branch Block (LBBB)

In both the minimal and maximal cohorts, only one Ranch Hand experienced LBBB. This Ranch Hand's serum dioxin measurement was 11.64 ppt which placed him in the low dioxin category under the minimal assumption and in the medium dioxin category under the maximal assumption in the initial dioxin and current dioxin with time since tour analyses. In the categorized current dioxin analysis, there were three Comparisons in the background category who were also diagnosed as having LBBB. However, the aforementioned Ranch Hand was not included in this analysis since his level of dioxin body burden fell between the

TABLE 12-11.

Analysis of ECG: Right Bundle Branch Block

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	0.0	1.21 (0.40,3.70)	0.737
	Medium	224	0.9		
	High	112	0.0		
b) Maximal (n=647)	Low	173	0.6	1.01 (0.43,2.34)	0.985
	Medium	320	0.3		
	High	154	0.7		

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
c) Minimal (n=446)	≤18.6	0.0 (59)	0.0 (113)	0.0 (46)	--	--
	>18.6	0.0 (49)	1.7 (115)	0.0 (64)	1.00 (0.31,3.20)	0.996[b]
d) Maximal (n=647)	≤18.6	1.0 (103)	0.0 (167)	0.0 (68)	--	--
	>18.6	0.0 (68)	1.3 (154)	0.0 (87)	1.29 (0.51,3.25)	0.595[b]

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

[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.

Note: Initial Dioxin: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

Current Dioxin: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-11. (Continued)

Analysis of ECG: Right Bundle Branch Block

e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	0.7	All Categories		0.467
Unknown	320	0.6	Unknown vs. Background	0.88 (0.17,4.55)	0.999
Low	177	1.1	Low vs. Background	1.60 (0.31,8.29)	0.854
High	155	0.0	High vs. Background	–	0.736
Total	1,355				

f) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.649	AGE (p=0.002) RACE (p=0.027)
Unknown	320	Unknown vs. Background	0.79 (0.14,4.38)	0.791	%BFAT (p=0.069)
Low	177	Low vs. Background	1.97 (0.37,10.60)	0.429	
High	155	High vs. Background	–	–	
Total	1,355				

--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

cutpoints of the unknown and low current dioxin categories. Due to the sparse number of abnormalities, relative risks, confidence intervals, and p-values are not presented (Table 12-12 [a-e]).

ECG: Nonspecific ST- and T-Wave Changes

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The analysis of the prevalence of nonspecific ST- and T-wave changes did not reveal a significant association with initial dioxin for the unadjusted minimal or maximal analyses (Table 12-13 [a] and [b]: p=0.347 and p=0.694). These nonsignificant results did not change after adjusting for significant covariates (Table 12-13 [c] and [d]: minimal, p=0.948; maximal, p=0.542).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of nonspecific ST- and T-wave changes, the interactions between current dioxin and time since tour were nonsignificant for both the minimal and maximal cohorts (Table 12-13 [e] and [f]: p=0.587 and p=0.848). The associations between current dioxin and the prevalence of nonspecific ST- and T-wave changes were also nonsignificant within the time strata under both minimal and maximal assumptions.

The adjusted minimal analysis of nonspecific ST- and T-wave changes displayed similar nonsignificant results (Table 12-13 [g]: p>0.40 for interaction and time-specific strata). Under the maximal assumption, the adjusted analysis of nonspecific ST- and T-wave changes revealed a significant interaction among current dioxin, time since tour, and age (Table 12-13 [h]: p=0.029). Appendix Table K-1 presents separate analyses for younger and older Ranch Hands in order to examine this interaction. The stratified analyses did not detect any significant results in either age stratum (p>0.15 for each interaction and time-specific stratum). The analysis of the younger Ranch Hands displayed nonsignificant negative associations between current dioxin and nonspecific ST- and T-waves within each time stratum. In contrast, the analysis of the older Ranch Hands exhibited nonsignificant positive associations within each time stratum.

The results of the maximal adjusted analyses of nonspecific ST- and T-wave changes were nonsignificant after the deletion of the current dioxin-by-time-by-age interaction (Table 12-13 [h]: p>0.60 for each analysis).

Results of Analyses Without Adjustment for Percent Body Fat. After excluding percent body fat from the maximal adjusted analysis of nonspecific ST- and T-wave changes, the interaction among current dioxin, time since tour, and age remained significant (Appendix Table K-2: p=0.015). Stratified analyses also changed very little (Appendix Table K-3). The analysis of older Ranch Hands with later tours became significant (Adj. RR=1.63, p=0.032).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In both the unadjusted and adjusted analyses, the prevalence of nonspecific ST- and T-wave changes did not differ significantly among the four current dioxin categories (Table

TABLE 12-12.

Analysis of ECG: Left Bundle Branch Block

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	n	Percent Abnormal
a) Minimal (n=446)	Low	110	0.9
	Medium	224	0.0
	High	112	0.0
b) Maximal (n=647)	Low	173	0.0
	Medium	320	0.3
	High	154	0.0

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High
c) Minimal (n=446)	≤18.6	0.0 (59)	0.0 (113)	0.0 (46)
	>18.6	2.0 (49)	0.0 (115)	0.0 (64)
d) Maximal (n=647)	≤18.6	0.0 (103)	0.0 (167)	0.0 (68)
	>18.6	0.0 (68)	0.7 (154)	0.0 (87)

Note: Initial Dioxin: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

Current Dioxin: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-12. (Continued)

Analysis of ECG: Left Bundle Branch Block

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	n	Percent Yes
Background	703	0.4
Unknown	320	0.0
Low	177	0.0
High	155	0.0
Total	1,355	

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 12-13.

Analysis of ECG: Nonspecific ST- and T-Wave Changes

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	11.8	0.89 (0.69,1.14)	0.347
	Medium	224	14.3		
	High	112	8.9		
b) Maximal (n=647)	Low	173	8.7	1.04 (0.87,1.24)	0.694
	Medium	320	12.8		
	High	154	9.7		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	0.99 (0.76,1.30)	0.948	AGE (p<0.001) RACE (p=0.010) PACKYR (p=0.013) %BFAT (p=0.003)
d) Maximal (n=647)	1.06 (0.87,1.30)	0.542	AGE (p<0.001) RACE (p=0.024) PACKYR (p=0.005) %BFAT (p=0.002)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-13. (Continued)

Analysis of ECG: Nonspecific ST- and T-Wave Changes

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.587[b]
	≤18.6	10.2 (59)	9.7 (113)	6.5 (46)	0.92 (0.58,1.45)	0.721[c]
	>18.6	18.4 (49)	14.8 (115)	14.1 (64)	0.79 (0.57,1.09)	0.153[c]
f) Maximal (n=647)						0.848[b]
	≤18.6	8.7 (103)	8.4 (167)	8.8 (68)	1.02 (0.75,1.39)	0.893[c]
	>18.6	10.3 (68)	14.9 (154)	13.8 (87)	0.98 (0.78,1.25)	0.889[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=446)			0.428[b]	AGE (p=0.001)
	≤18.6	1.12 (0.70,1.81)	0.636[c]	RACE (p=0.012)
	>18.6	0.89 (0.63,1.25)	0.499[c]	PACKYR (p=0.015)
				%BFAT (p=0.003)
h) Maximal (n=647)			0.823**[b]	CURR*TIME*AGE (p=0.029)
	≤18.6	1.08 (0.77,1.52)**	0.645**[c]	RACE (p=0.042)
	>18.6	1.03 (0.80,1.33)**	0.799**[c]	PACKYR (p=0.007)
				%BFAT (p=0.004)

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-13. (Continued)

Analysis of ECG: Nonspecific ST- and T-Wave Changes

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	10.8	All Categories		0.308
Unknown	320	7.8	Unknown vs. Background	0.70 (0.44,1.12)	0.138
Low	177	12.4	Low vs. Background	1.17 (0.71,1.94)	0.541
High	155	11.6	High vs. Background	1.08 (0.63,1.87)	0.772
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.297	AGE (p<0.001) RACE (p=0.047)
Unknown	320	Unknown vs. Background	0.75 (0.46,1.22)	0.246	PACKYR (p=0.019)
Low	177	Low vs. Background	1.20 (0.71,2.01)	0.492	%BFAT (p=0.010)
High	155	High vs. Background	1.35 (0.76,2.39)	0.299	
Total	1,355				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

12-13 [i] and [j]: p>0.10 for each contrast). The percentages of nonspecific ST- and T-wave changes were higher for Ranch Hands in the low and high current dioxin categories than for Comparisons in the background category (background, 10.8%; unknown, 7.8%; low, 12.4%; high, 11.6%).

ECG: Bradycardia

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the prevalence of bradycardia was not related significantly to initial dioxin (Table 12-14 [a]: p=0.298) in the unadjusted analysis. The maximal unadjusted analysis detected a marginally significant negative association between initial dioxin and bradycardia (Table 12-14 [b]: Adj. RR=0.75, p=0.092). The relative frequencies of Ranch Hands diagnosed with bradycardia were 5.8, 3.4, and 2.0 percent for the low, medium, and high initial dioxin categories in the maximal cohort.

The minimal analysis of bradycardia remained nonsignificant after adjustment for percent body fat (Table 12-14 [c]: p=0.393). Similarly, after adjustment for covariate information, the maximal analysis again displayed a marginally significant negative association between initial dioxin and bradycardia (Table 12-14 [d]: Adj. RR=0.75, p=0.096).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal assumption, the unadjusted analysis of bradycardia displayed a nonsignificant interaction between current dioxin and time since tour (Table 12-14 [e]: p=0.363). In contrast, the maximal unadjusted analysis revealed a marginally significant current dioxin-by-time interaction (Table 12-14 [f]: p=0.067). The analysis of Ranch Hands with 18.6 years or less since tour displayed a nonsignificant positive association between current dioxin and bradycardia (Adj. RR=1.02, p=0.905), while for those with more than 18.6 years since tour, there was a marginally significant negative association (Adj. RR=0.46, p=0.076). For the maximal cohort, the relative frequencies of Ranch Hands with early tours who were diagnosed with bradycardia were 5.9 percent and 2.0 percent for low and medium current dioxin; there were no Ranch Hands with bradycardia for high current dioxin in this stratum.

After adjusting the minimal analysis of bradycardia for percent body fat, the results remained nonsignificant (Table 12-14 [g]: p>0.35 for each analysis). Similarly, the adjustment for race and lifetime alcohol history did not change the marginal significance of the current dioxin-by-time since tour interaction under the maximal assumption (Table 12-14 [h]: p=0.051). The positive association between current dioxin and bradycardia remained nonsignificant for Ranch Hands with later tours (Adj. RR=1.05, p=0.829); the negative association for Ranch Hands with early tours also remained marginally significant (Adj. RR=0.44, p=0.063).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis did not detect any significant differences in the prevalence of bradycardia among the four current dioxin categories (Table 12-14 [i]: p=0.184).

TABLE 12-14.

Analysis of ECG: Bradycardia

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	3.6	0.77 (0.46,1.29)	0.298
	Medium	224	3.6		
	High	112	1.8		
b) Maximal (n=647)	Low	173	5.8	0.75 (0.53,1.07)	0.092
	Medium	320	3.4		
	High	154	2.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	0.80 (0.47,1.36)	0.393	%BFAT (p=0.109)
d) Maximal (n=638)	0.75 (0.53,1.07)	0.096	RACE (p=0.107) DRKYR (p=0.096)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-14. (Continued)

Analysis of ECG: Bradycardia

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.363[b]
(n=446)	≤18.6	6.8 (59)	4.4 (113)	4.4 (46)	1.03 (0.58,1.83)	0.930[c]
	>18.6	0.0 (49)	2.6 (115)	0.0 (64)	0.56 (0.15,2.05)	0.379[c]
f) Maximal						0.067[b]
(n=647)	≤18.6	5.8 (103)	4.2 (167)	5.9 (68)	1.02 (0.69,1.52)	0.905[c]
	>18.6	5.9 (68)	2.0 (154)	0.0 (87)	0.46 (0.20,1.08)	0.076[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.361[b]	%BFAT (p=0.102)
(n=446)	≤18.6	1.08 (0.60,1.95)	0.802[c]	
	>18.6	0.58 (0.15,2.17)	0.417[c]	
h) Maximal			0.051[b]	RACE (p=0.076)
(n=638)	≤18.6	1.05 (0.70,1.56)	0.829[c]	DRKYR (p=0.118)
	>18.6	0.44 (0.19,1.05)	0.063[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-14. (Continued)

Analysis of ECG: Bradycardia

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	5.8	All Categories		0.184
Unknown	320	5.9	Unknown vs. Background	1.02 (0.58,1.79)	0.947
Low	177	3.4	Low vs. Background	0.57 (0.24,1.36)	0.202
High	155	2.6	High vs. Background	0.43 (0.15,1.21)	0.110
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	667	All Categories		0.256**	DXCAT*RACE (p=0.029)
Unknown	303	Unknown vs. Background	1.01 (0.56,1.81)**	0.986**	PACKYR (p=0.006)
Low	174	Low vs. Background	0.57 (0.24,1.39)**	0.217**	%BFAT (p=0.064)
High	150	High vs. Background	0.45 (0.16,1.30)**	0.141**	DIFCORT (p=0.018)
Total	1,294				HRTDIS (p=0.045)

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

The adjusted analysis of bradycardia revealed a significant interaction between categorized current dioxin and race (Table 12-14 [j]: p=0.029). Stratified analyses were performed to investigate this interaction (Appendix Table K-1). Within the Black stratum, there were only three Ranch Hands with bradycardia (two in the unknown category and one in the low category) and no Comparisons. Due to this sparse number of abnormalities, adjusted relative risks and confidence intervals were not presented. However, in an unadjusted analysis of the Black stratum, the contrast of the Ranch Hands in the unknown category versus the Comparisons in the background category was marginally significant (p=0.080). The analysis of the non-Black stratum did not detect any significant differences in the prevalence of bradycardia among the four current dioxin categories (p>0.10 for each contrast). However, the percentages of Ranch Hands with bradycardia in the unknown (5.5%), low (3.0%), and high (2.8%) categories were all lower than the corresponding percentage of Comparisons in the background category (6.2%).

After deletion of the categorized current dioxin-by-race interaction from the adjusted model, the analysis of bradycardia did not find any significant differences among the four current dioxin categories (Table 12-14 [j]: p>0.10 for each contrast).

Results of Analyses Without Adjustment for Percent Body Fat. The exclusion of percent body fat from the adjusted analysis of bradycardia did not change the significance of the categorized current dioxin-by-race interaction (Appendix Table K-2: p=0.025). The stratified analyses of this interaction also changed very little. However, within the non-Black stratum, the contrast of Ranch Hands in the high current dioxin category versus Comparisons in the background category became marginally significant with the Ranch Hands having a lower risk of bradycardia relative to the Comparisons (Appendix Table K-3: Adj. RR=0.40, 95% C.I.: [0.14,1.14], p=0.087).

Similarly, after deletion of percent body fat and the categorized current dioxin-by-race interaction from the adjusted model, the contrast of the prevalence of bradycardia in Ranch Hands in the high category versus Comparisons in the background category became marginally significant (Appendix Table K-2: Adj. RR=0.51, 95% C.I.: [0.14,1.17], p=0.095). The other contrasts in the analysis remained nonsignificant.

ECG: Arrhythmia

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analysis of the prevalence of arrhythmia did not detect a significant association with initial dioxin under either assumption (Table 12-15 [a] and [b]: minimal, p=0.270; maximal, p=0.601).

The minimal adjusted analysis of arrhythmia revealed a significant interaction between initial dioxin and personality type (Table 12-15 [c]: p=0.036). Stratified analyses detected a significant positive association between initial dioxin and arrhythmia for type A Ranch Hands (Appendix Table K-1: Adj. RR=2.54, p=0.005) and a nonsignificant positive association for type B Ranch Hands (Adj. RR=1.06, p=0.837). The relative frequencies of type A Ranch Hands diagnosed with arrhythmia were 1.9, 1.1, and 9.1 percent for the low, medium, and high initial dioxin categories.

TABLE 12-15.

Analysis of ECG: Arrhythmia

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	1.8	1.25 (0.85,1.84)	0.270
	Medium	224	4.5		
	High	112	4.5		
b) Maximal (n=647)	Low	173	4.6	1.08 (0.81,1.43)	0.601
	Medium	320	3.1		
	High	154	5.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=433)	1.43 (0.96,2.13)**	0.092**	INIT*PERS (p=0.036) AGE (p<0.001) PACKYR (p=0.093)
d) Maximal (n=617)	1.23 (0.91,1.66)	0.186	AGE (p=0.003) DRKYR (p=0.109) DIFCORT (p=0.051)

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

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-15. (Continued)

Analysis of ECG: Arrhythmia

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.339[b]
(n=446)	≤18.6	1.7 (59)	2.7 (113)	8.7 (46)	1.55 (0.85,2.83)	0.149[c]
	>18.6	2.0 (49)	5.2 (115)	3.1 (64)	1.05 (0.61,1.81)	0.867[c]
f) Maximal						0.032[b]
(n=647)	≤18.6	1.9 (103)	1.8 (167)	7.4 (68)	1.51 (0.96,2.37)	0.074[c]
	>18.6	10.3 (68)	3.9 (154)	3.5 (87)	0.78 (0.51,1.17)	0.230[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.201[b]	AGE (p<0.001)
(n=446)	≤18.6	2.18 (1.15,4.15)	0.017[c]	
	>18.6	1.28 (0.75,2.21)	0.366[c]	
h) Maximal			0.034**[b]	CURR*TIME*DIFCORT
(n=617)	≤18.6	1.79 (1.11,2.90)**	0.018**[c]	(p=0.033)
	>18.6	0.90 (0.58,1.40)**	0.648**[c]	AGE (p=0.008) DRKYR (p=0.062)

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-15. (Continued)

Analysis of ECG: Arrhythmia

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	3.7	All Categories		0.626
Unknown	320	4.7	Unknown vs. Background	1.28 (0.67,2.45)	0.456
Low	177	2.8	Low vs. Background	0.76 (0.29,2.00)	0.574
High	155	5.2	High vs. Background	1.42 (0.63,3.19)	0.400
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	667	All Categories		0.238	AGE (p<0.001) DIFCORT (p=0.048)
Unknown	303	Unknown vs. Background	1.33 (0.68,2.58)	0.404	
Low	174	Low vs. Background	0.83 (0.31,2.23)	0.712	
High	150	High vs. Background	2.34 (1.00,5.51)	0.051	
Total	1,294				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

After deletion of the initial dioxin-by-personality type interaction and adjusting only for age, lifetime cigarette smoking history, and personality type, the minimal analysis displayed a marginally significant positive association between initial dioxin and the prevalence of arrhythmia in Ranch Hands (Table 12-15 [c]: Adj. RR=1.43, p=0.092). The percentages of Ranch Hands in the minimal cohort with arrhythmia were 1.8, 4.5, and 4.5 percent for the low, medium, and high initial dioxin categories.

The findings of the maximal adjusted analysis concurred with the unadjusted results in the lack of significance of the relationship between initial dioxin and the prevalence of arrhythmia (Table 12-15 [d]: p=0.186).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of arrhythmia under the minimal assumption, the interaction between current dioxin and time since tour was not significant (Table 12-15 [e]: p=0.339). Based on the maximal assumption, the associations between current dioxin and arrhythmia differed significantly for the two time strata in the unadjusted analysis (Table 12-15 [f]: p=0.032). For Ranch Hands with 18.6 years or less since tour, there was a marginally significant positive relationship between current dioxin and arrhythmia (Adj. RR=1.51, p=0.074). Within the time greater than 18.6 years stratum, there was a nonsignificant negative association between current dioxin and arrhythmia (Adj. RR=0.78, p=0.230). The relative frequencies of Ranch Hands with later tours who were diagnosed with arrhythmia were 1.9, 1.8, and 7.4 percent for low, medium, and high current dioxin.

After adjusting for age in the minimal analysis of arrhythmia, the interaction between current dioxin and time since tour remained nonsignificant (Table 12-15 [g]: p=0.201). However, for Ranch Hands with later tours, the positive association between current dioxin and the prevalence of arrhythmia became significant (Adj. RR=2.18, p=0.017). In the stratum of Ranch Hands with early tours, the positive association remained nonsignificant (p=0.366). For the Ranch Hands with 18.6 years or less since tour, the percentages of arrhythmia in the low, medium, and high current dioxin categories were 1.7, 2.7, and 8.7 percent.

The adjusted maximal analysis revealed a significant interaction among current dioxin, time since tour, and differential cortisol response (Table 12-15 [h]: p=0.033). To examine this interaction, analyses were performed separately for each differential cortisol-response stratum (Appendix Table K-1). For Ranch Hands with a differential cortisol response of 0.6 µg/dl or less, the interaction between current dioxin and time was not significant (p=0.314). However, there was a marginally significant positive association between current dioxin and arrhythmia for Ranch Hands with late tours (Adj. RR=1.97, p=0.086) and a nonsignificant positive association for Ranch Hands with early tours (Adj. RR=1.08, p=0.888). Within the 18.6 years or less time stratum, there were no Ranch Hands with arrhythmia for the low current dioxin classification; the relative frequencies of arrhythmia for the medium and high classifications were 5.7 and 10.0 percent.

In the stratified analysis of Ranch Hands with a differential cortisol response between 0.6 µg/dl and 4.0 µg/dl, there was only one Ranch Hand diagnosed with arrhythmia (high current dioxin) in the 18.6 years or less time stratum. In the greater than 18.6 years time stratum, there was a marginally significant negative association between current dioxin and

arrhythmia (Adj. RR=0.36, p=0.077). The percentages of Ranch Hands diagnosed with arrhythmia in this time stratum were 12.0 and 5.8 percent for low and medium current dioxin; there were no Ranch Hands in the high current dioxin classification with arrhythmia.

For Ranch Hands with a differential cortisol response greater than 4.0 μg/dl, the analysis displayed nonsignificant positive relationships between current dioxin and arrhythmia for the two time strata, which were not significantly different (Appendix Table K-1: p>0.15 for the interaction and time-specific strata).

After deletion of the interaction and adjustment for only age, lifetime alcohol history, and differential cortisol response, the maximal analysis detected a significant interaction between current dioxin and time (Table 12-15 [h]: p=0.034). The analysis also revealed a significant positive association between current dioxin and arrhythmia for Ranch Hands with later tours (Adj. RR=1.79, p=0.018) and a nonsignificant negative association for Ranch Hands with early tours (Adj. RR=0.90, p=0.648).

Longitudinal analyses of the overall ECG displayed significant negative associations with dioxin.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the prevalence of arrhythmia did not detect any significant differences among the four current dioxin categories (Table 12-15 [i]: p>0.35 for each contrast).

In the analysis of arrhythmia, the adjustment for age and differential cortisol response did not change the lack of significance of the overall contrast of the four current dioxin categories (Table 12-15 [j]: p=0.238). However, the contrast of the Ranch Hands in the high category versus the Comparisons in the background category became marginally significant with the Ranch Hands having a higher risk of arrhythmia than the Comparisons (Adj. RR=2.34, 95% C.I.: [1.00,5.51], p=0.051). The relative frequencies of participants diagnosed with arrhythmia were 3.7, 4.7, 2.8, and 5.2 percent for the background, unknown, low, and high current dioxin categories.

ECG: Other Diagnoses

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Neither the unadjusted nor the adjusted analysis detected significant associations between initial dioxin and other ECG diagnoses under the minimal and maximal assumptions (Table 12-16 [a-d]: p>0.10 for each analysis).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Based on the minimal assumption, the unadjusted analysis of other ECG diagnoses did not detect a significant current dioxin-by-time since tour interaction (Table 12-16 [e]: p=0.129). However, for Ranch Hands with greater than 18.6 years since tour, there was a significant negative association between current dioxin and other abnormal ECG diagnoses

TABLE 12-16.

Analysis of ECG: Other Diagnoses

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	17.3	0.85 (0.67,1.07)	0.146
	Medium	224	18.3		
	High	112	10.7		
b) Maximal (n=647)	Low	173	19.1	0.88 (0.75,1.04)	0.122
	Medium	320	19.1		
	High	154	11.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=446)	0.90 (0.71,1.15)	0.396	AGE (p=0.019)
d) Maximal (n=638)	0.93 (0.78,1.09)	0.365	AGE (p=0.002) DRKYR (p=0.143)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-16. (Continued)

Analysis of ECG: Other Diagnoses

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.129[b]
	≤18.6	13.6 (59)	22.1 (113)	13.0 (46)	1.01 (0.73,1.41)	0.942[c]
	>18.6	24.5 (49)	13.9 (115)	7.8 (64)	0.70 (0.49,1.00)	0.048[c]
f) Maximal (n=647)						0.040[b]
	≤18.6	16.5 (103)	19.8 (167)	13.2 (68)	1.03 (0.82,1.29)	0.814[c]
	>18.6	22.1 (68)	20.1 (154)	6.9 (87)	0.72 (0.56,0.93)	0.011[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=440)			0.120[b]	AGE (p=0.013)
	≤18.6	1.15 (0.81,1.63)	0.428[c]	DRKYR (p=0.141)
	>18.6	0.78 (0.55,1.12)	0.185[c]	
h) Maximal (n=638)			0.026[b]	AGE (p=0.002)
	≤18.6	1.13 (0.89,1.44)	0.305[c]	DRKYR (p=0.109)
	>18.6	0.77 (0.59,1.00)	0.046[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-16. (Continued)

Analysis of ECG: Other Diagnoses

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	18.9	All Categories		0.024
Unknown	320	19.1	Unknown vs. Background	1.01 (0.72,1.41)	0.957
Low	177	19.8	Low vs. Background	1.06 (0.70,1.60)	0.796
High	155	9.7	High vs. Background	0.46 (0.26,0.81)	0.007
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	664	All Categories		0.140	AGE (p<0.001)
Unknown	302	Unknown vs. Background	0.95 (0.67,1.35)	0.776	CHOL (p=0.042)
Low	172	Low vs. Background	1.07 (0.70,1.64)	0.751	PERS (p=0.081)
High	149	High vs. Background	0.53 (0.29,0.96)	0.036	
Total	1,287				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

(Est. RR=0.70, p=0.048). Within this stratum, the percentages of Ranch Hands with other abnormal ECG diagnoses decreased as current dioxin increased (low, 24.5%; medium, 13.9%; high, 7.8%).

The maximal unadjusted analysis revealed that the association between current dioxin and other ECG diagnoses differed significantly between the time strata (Table 12-16 [f]: p=0.040). For Ranch Hands with later tours, there was a nonsignificant positive relationship between current dioxin and other ECG diagnoses (Adj. RR=1.03, p=0.814). In contrast, there was a significant negative association for Ranch Hands with early tours (Adj. RR=0.72, p=0.011). Similar to the minimal unadjusted analysis, within the time greater than 18.6 years stratum of the maximal cohort, the percentages of Ranch Hands with other abnormal ECG diagnoses decreased with increasing levels of dioxin (low, 22.1%; medium, 20.1%; high, 6.9%).

After adjusting for age and lifetime alcohol history, the minimal analysis of other ECG diagnoses did not detect any significant results (Table 12-16 [g]: p>0.10 for interaction and time-specific analyses). Under the maximal assumption, the current dioxin-by-time since tour interaction remained significant after including the same covariates (Table 12-16 [h]: p=0.026). Also, the negative association between current dioxin and the prevalence of other ECG diagnoses remained nonsignificant for Ranch Hands with more than 18.6 years since tour (Adj. RR=0.77, p=0.046).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of the prevalence of other abnormal ECG diagnoses, the simultaneous contrast of the four current dioxin categories was significant (Table 12-16 [i]: p=0.024). The percentages of participants with other abnormal ECG diagnoses were nearly equivalent for the background, unknown, and low current dioxin categories (18.9%, 19.1%, and 19.8%), but the percentage of the Ranch Hands in the high category was much lower (9.7%). In fact, the Ranch Hands in the high category had a significantly lower risk of other abnormal ECG diagnoses relative to the Comparisons in the background category (Est. RR=0.46, 95% C.I.: [0.26,0.81], p=0.007).

After adjusting for age, cholesterol, and personality type, the analysis of other ECG diagnoses did not detect a significant overall difference among the four current dioxin categories (Table 12-16 [j]: p=0.140). However, the Ranch Hands in the high current dioxin category had a significantly lower risk of other abnormal ECG diagnoses relative to the Comparisons in the background category (Adj. RR=0.53, 95% C.I.: [0.29,0.96], p=0.036).

Physical Examination: Peripheral Vascular Function Variables

Diastolic Blood Pressure (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the unadjusted analyses of diastolic blood pressure in its continuous form did not detect a significant association with initial dioxin (Table 12-17 [a] and [b]: p=0.640 and p=0.176).

TABLE 12-17.

Analysis of Diastolic Blood Pressure (mm Hg) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal (n=446) (R^2<0.001)	Low	110	75.02	0.172 (0.367)	0.640
	Medium	224	76.48		
	High	112	75.62		
b) Maximal (n=647) (R^2=0.003)	Low	173	74.61	0.359 (0.265)	0.176
	Medium	320	75.79		
	High	154	76.09		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c) Minimal (n=431) (R^2=0.068)	Low	107	77.74	0.119 (0.369)	0.748	RACE (p=0.013) CHOL (p=0.008) %BFAT (p=0.005) PERS (p=0.026) HRTDIS (p=0.019)
	Medium	217	79.59			
	High	107	78.28			
d) Maximal (n=621) (R^2=0.069)	Low	163	****	****	****	INIT*PERS (p=0.002) RACE (p=0.013) CHOL (p=0.003) %BFAT (p<0.001)
	Medium	310	****			
	High	148	****			

[a]Slope and standard error based on diastolic blood pressure versus log_2 dioxin.

****Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, and p-value not presented.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-17. (Continued)

Analysis of Diastolic Blood Pressure (mm Hg) (Continuous)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Mean/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[a]	p-Value
e) Minimal (n=446) (R^2=0.004)	≤18.6	74.19 (59)	76.18 (113)	74.67 (46)	0.188 (0.583)	0.884[b] 0.747[c]
	>18.6	75.65 (49)	77.12 (115)	75.89 (64)	0.077 (0.494)	0.877[c]
f) Maximal (n=647) (R^2=0.004)	≤18.6	74.85 (103)	75.45 (167)	74.82 (68)	0.180 (0.402)	0.680[b] 0.655[c]
	>18.6	74.87 (68)	75.81 (154)	77.18 (87)	0.406 (0.373)	0.277[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
g) Minimal (n=431) (R^2=0.072)	≤18.6	76.91 (56)	78.99 (109)	78.04 (42)	0.370 (0.599)	0.543[b] 0.537[c]	RACE (p=0.015) CHOL (p=0.008) %BFAT (p=0.005)
	>18.6	78.54 (48)	79.99 (113)	78.16 (63)	-0.098 (0.489)	0.842[c]	PERS (p=0.030) HRTDIS (p=0.019)
h) Maximal (n=643) (R^2=0.054)	≤18.6	77.26 (102)	77.18 (165)	76.60 (67)	-0.026 (0.401)	0.692[b] 0.949[c]	RACE (p=0.017) CHOL (p=0.003) %BFAT (p<0.001)
	>18.6	76.97 (68)	77.56 (154)	78.36 (87)	0.188 (0.368)	0.610[c]	

[a]Slope and standard error based on diastolic blood pressure versus log_2 dioxin.

[b]Test of significance for homogeneity of slopes (current dioxin continuous, time categorized).

[c]Test of significance for slope equal to 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-17. (Continued)

Analysis of Diastolic Blood Pressure (mm Hg) (Continuous)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Mean	Contrast	Difference of Means (95% C.I.)	p-Value
Background	703	74.54	All Categories		0.017
Unknown	320	74.04	Unknown vs. Background	-0.50 (-1.72,0.73)	0.429
Low	177	76.25	Low vs. Background	1.71 (0.18,3.24)	0.028
High	155	76.15	High vs. Background	1.61 (0.00,3.23)	0.051
Total	1,355		(R^2=0.008)		

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	659	74.54***	All Categories		0.062***	DXCAT*PERS (p=0.007)
Unknown	297	74.36***	Unknown vs. Background	-0.19 (-1.45,1.07)***	0.772***	DXCAT*HRTDIS
Low	170	76.22***	Low vs. Background	1.68 (0.15,3.20)***	0.032***	(p=0.014)
High	143	75.96***	High vs. Background	1.42 (-0.26,3.09)***	0.098***	AGE (p=0.035)
Total	1,269		(R^2=0.089)			DRKYR (p=0.022)
						CHOL (p=0.001)
						%BFAT (p<0.001)
						DIFCORT (p=0.018)

***Categorized current dioxin-by-covariate interaction ($p \leq 0.01$); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of these interactions.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

After adjustment for covariate information, the association between diastolic blood pressure and initial dioxin in its continuous form remained nonsignificant in the minimal analysis (Table 12-17 [c]: p=0.748). The adjusted maximal analysis revealed a significant interaction between initial dioxin and personality type (Table 12-17 [d]: p=0.002). Stratified analyses detected a marginally significant negative association between initial dioxin and diastolic blood pressure for type A Ranch Hands (Appendix Table K-1: p=0.060) and a significant positive association for type B Ranch Hands (p=0.015). The adjusted mean diastolic blood pressure values for type A Ranch Hands were 77.99, 77.21, and 75.85 mm Hg for the low, medium, and high initial dioxin categories. The corresponding means for type B Ranch Hands were 75.97, 77.96, and 79.30 mm Hg, respectively.

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. The maximal analysis of diastolic blood pressure in its continuous form without cholesterol and percent body fat in the model also revealed a significant initial dioxin-by-personality type interaction (Appendix Table K-2: p=0.005). In the stratified analyses of this interaction, the decreasing association between initial dioxin and diastolic blood pressure for type A Ranch Hands became nonsignificant (Appendix Table K-3: p=0.263) after the exclusion of cholesterol and percent body fat from the model. The positive association between initial dioxin and diastolic blood pressure remained significant for type B Ranch Hands (p=0.003).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal and the maximal assumptions, the association between current dioxin and diastolic blood pressure did not differ significantly between time since tour strata for the unadjusted or adjusted analyses (Table 12-17 [e-h]: p>0.50 for each analysis). The associations between current dioxin and diastolic blood pressure also were nonsignificant within the time strata in the minimal and maximal unadjusted and adjusted analyses.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of diastolic blood pressure in its continuous form detected a significant difference among the four current dioxin categories (Table 12-17 [i]: p=0.017). Specifically, the unadjusted mean diastolic blood pressure of the Ranch Hands in the low category was significantly higher than the corresponding mean of the Comparisons in the background category (p=0.028). Also, the unadjusted mean diastolic blood pressure of the Ranch Hands in the high category was marginally higher than the corresponding mean of the Comparisons (p=0.051). The unadjusted mean diastolic blood pressures for participants in the background, unknown, low, and high current dioxin categories were 74.54, 74.04, 76.25, and 76.15 mm Hg.

The adjusted analysis of diastolic blood pressure revealed significant interactions between categorized current dioxin and personality type and between categorized current dioxin and family history of heart disease (Table 12-17 [j]: p=0.007 and p=0.014). In order to investigate these interactions, separate analyses were performed for each stratum combination of family history of heart disease and personality type (Appendix Table K-1). For type A participants with and without a family history of heart disease, there were no significant differences in the mean diastolic blood pressures of the four current dioxin categories (p>0.25 for each contrast).

The stratified analysis of type B participants with a family history of heart disease detected a significant difference among the mean diastolic blood pressures of the four current dioxin categories (Appendix Table K-1: $p<0.001$). Specifically, the mean diastolic blood pressure of the Ranch Hands in the low category was significantly higher than the corresponding mean of the Comparisons in the background category ($p<0.001$). Also, the mean of the Ranch Hands in the high category was marginally greater than the mean of the Comparisons in the background category ($p=0.061$). The adjusted mean diastolic blood pressures of the background, unknown, low, and high current dioxin categories were 74.10, 71.73, 81.02, and 78.39 mm Hg.

For type B participants without a family history of heart disease, the overall contrast of the mean diastolic blood pressures of the four current dioxin categories was marginally significant (Appendix Table K-1: $p=0.065$). The Ranch Hands in the high current dioxin category had a significantly higher mean diastolic blood pressure than the Comparisons in the background category ($p=0.016$). The adjusted mean diastolic blood pressures of the participants in the background, unknown, low, and high current dioxin categories were 74.22, 73.58, 74.94, and 77.28 mm Hg.

After deletion of the categorized current dioxin-by-covariate interactions from the model, the overall contrast of the mean diastolic blood pressures of the four current dioxin categories was marginally significant (Table 12-17 [j]: $p=0.062$). Similar to the unadjusted analysis, the Ranch Hands in the low category had a significantly higher mean diastolic blood pressure than the Comparisons in the background category ($p=0.032$), and the Ranch Hands in the high current dioxin category had a marginally greater mean diastolic blood pressure than the Comparisons ($p=0.098$).

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. After removing cholesterol and percent body fat from the adjusted analysis of diastolic blood pressure in its continuous form, the interactions between categorized current dioxin and personality type and between categorized current dioxin and family history of heart disease remained significant (Appendix Table K-2: $p=0.012$ and $p=0.011$, respectively). In the stratified analyses excluding cholesterol and percent body fat for type A participants with a family history of heart disease, the contrast of the Comparisons in the background category and the Ranch Hands in the low category became marginally significant (Appendix Table K-3: $p=0.083$) with the Ranch Hands having a higher mean diastolic blood pressure. The adjusted mean diastolic blood pressures for this stratum were 74.79, 73.76, 79.60, and 75.50 mm Hg for the background, unknown, low, and high current dioxin categories. The results remained nonsignificant for the type A participants with no family history of heart disease.

For type B participants with a family history of heart disease, the contrast of the Ranch Hands in the unknown category versus the Comparisons in the background category became marginally significant (Appendix Table K-3: $p=0.087$) with the Ranch Hands having a lower mean diastolic blood pressure. However, the contrast of the Ranch Hands versus the Comparisons in the high category became nonsignificant ($p=0.187$). Also, for type B participants with no history of heart disease in the family, the overall contrast of the mean diastolic blood pressures of the four current dioxin categories became significant ($p=0.002$) with Ranch Hands in the high current dioxin category having a significantly higher mean than the Comparisons ($p=0.002$).

In the model without the categorized current dioxin-by-covariate interactions, the exclusion of cholesterol and percent body fat increased the significance of the contrast of the mean diastolic blood pressure of the Ranch Hands in the high category versus the corresponding mean of the Comparisons in the background category (Appendix Table K-2: p=0.017).

Diastolic Blood Pressure (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Neither the unadjusted minimal nor maximal analysis detected a significant association between initial dioxin and discretized diastolic blood pressure (Table 12-18: [a] and [b]: p=0.784 and p=0.728, respectively).

After adjusting for covariate information, the minimal and maximal analyses also displayed nonsignificant results (Table 12-18 [c] and [d]: p=0.394 and p=0.751, respectively).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The associations between current dioxin and the prevalence of abnormally high diastolic blood pressure did not differ significantly with time since tour for either the unadjusted or adjusted minimal and maximal analyses (Table 12-18 [e-h]: p>0.35 for each interaction).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted and adjusted analyses of discretized diastolic blood pressure, the simultaneous contrast of the four current dioxin categories was nonsignificant (Table 12-18 [i] and [j]: p=0.301 and p=0.413, respectively). The Ranch Hands versus Comparisons contrasts were also nonsignificant.

Funduscopic Examination

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, the association between the frequency of abnormalities in small blood vessels detected by the funduscopic examination and initial dioxin was not significant for either the minimal or the maximal cohort (Table 12-19 [a] and [b]: p=0.727 and p=0.868). Adjusted analyses were not performed due to the sparse number of abnormalities.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Similar to the initial dioxin analyses, the unadjusted current dioxin and time since tour analyses of the prevalence of abnormal funduscopic examinations displayed nonsignificant results for Ranch Hands with later tours in the minimal and maximal cohorts (Table 12-19 [c] and [d]: p=0.458 and p=0.749). Due to the sparse number of abnormalities, adjusted analyses were not conducted.

TABLE 12-18.

Analysis of Diastolic Blood Pressure (Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	4.6	0.95 (0.67,1.36)	0.784
	Medium	224	7.1		
	High	112	3.6		
b) Maximal (n=647)	Low	173	4.1	1.05 (0.81,1.36)	0.728
	Medium	320	5.3		
	High	154	5.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=443)	0.85 (0.58,1.25)	0.394	AGE (p=0.033) CHOL (p=0.005) HRTDIS (p=0.045)
d) Maximal (n=643)	1.04 (0.80,1.35)	0.751	CHOL (p=0.075)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-18. (Continued)

Analysis of Diastolic Blood Pressure (Discrete)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)						0.963[b]
	≤18.6	3.4 (59)	6.2 (113)	2.2 (46)	0.94 (0.50,1.75)	0.835[c]
	>18.6	6.1 (49)	7.8 (115)	4.7 (64)	0.95 (0.61,1.49)	0.832[c]
f) Maximal (n=647)						0.547[b]
	≤18.6	4.9 (103)	4.2 (167)	4.4 (68)	0.95 (0.62,1.47)	0.829[c]
	>18.6	2.9 (68)	6.5 (154)	5.8 (87)	1.13 (0.80,1.58)	0.488[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=443)			0.978[b]	AGE (p=0.018)
	≤18.6	0.79 (0.40,1.56)	0.502[c]	CHOL (p=0.004)
	>18.6	0.80 (0.49,1.31)	0.381[c]	HRTDIS (p=0.048)
h) Maximal (n=643)			0.556[b]	CHOL (p=0.078)
	≤18.6	0.95 (0.62,1.48)	0.832[c]	
	>18.6	1.12 (0.80,1.57)	0.495[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-18. (Continued)

Analysis of Diastolic Blood Pressure (Discrete)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	4.3	All Categories		0.301
Unknown	320	3.1	Unknown vs. Background	0.72 (0.35,1.50)	0.384
Low	177	6.8	Low vs. Background	1.63 (0.82,3.26)	0.165
High	155	5.2	High vs. Background	1.22 (0.55,2.72)	0.625
Total	1,355				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.413	PACKYR (p=0.078)
Unknown	320	Unknown vs. Background	0.78 (0.37,1.62)	0.501	%BFAT (p=0.078)
Low	177	Low vs. Background	1.61 (0.80,3.22)	0.180	
High	155	High vs. Background	1.17 (0.52,2.63)	0.701	
Total	1,355				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 12-19.

Analysis of Funduscopic Examination

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	0.0	1.22 (0.40,3.72)	0.727
	Medium	224	0.9		
	High	112	0.0		
b) Maximal (n=647)	Low	173	1.2	0.94 (0.44,1.99)	0.868
	Medium	320	0.3		
	High	154	0.7		

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
c) Minimal (n=446)	≤18.6	0.0 (59)	0.9 (113)	2.2 (46)	1.58 (0.49,5.06)	-- 0.458[b]
	>18.6	0.0 (49)	0.0 (115)	0.0 (64)	--	--
d) Maximal (n=647)	≤18.6	1.0 (103)	1.2 (167)	1.5 (68)	1.13 (0.53,2.43)	-- 0.749[b]
	>18.6	0.0 (68)	0.0 (154)	0.0 (87)	--	--

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.
Note: Initial Dioxin: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

Current Dioxin: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-19. (Continued)

Analysis of Funduscopic Examination

e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	0.6	All Categories		0.922
Unknown	320	0.9	Unknown vs. Background	1.65 (0.37,7.43)	0.764
Low	177	0.6	Low vs. Background	0.99 (0.11,8.94)	0.999
High	155	0.7	High vs. Background	1.14 (0.13,10.22)	0.999
Total	1,355				

f) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	667	All Categories		0.892**	DXCAT*DIFCORT (p=0.024)
Unknown	303	Unknown vs. Background	1.70 (0.37,7.85)**	0.496**	AGE (p=0.028)
Low	174	Low vs. Background	0.94 (0.10,8.57)**	0.953**	HRTDIS (p=0.117)
High	150	High vs. Background	1.72 (0.18,16.74)**	0.639**	
Total	1,294				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis, there were no significant differences in the prevalence of abnormal findings in the funduscopic examinations among the four current dioxin categories (Table 12-19 [e]: p>0.75 for each contrast).

The adjusted analysis of the results of the funduscopic examination revealed a significant interaction between categorized current dioxin and differential cortisol response (Table 12-19 [f]: p=0.024). The stratified analyses showed very few participants with abnormal funduscopic examinations for each differential cortisol response classification (Appendix Table K-1). For participants with a differential cortisol response of 0.6 μg/dl or less, only four Comparisons in the background category and one Ranch Hand in the unknown category had abnormal funduscopic examination findings. Thus, the overall contrast of the four current dioxin categories was not significant (p=0.476), nor was the individual contrast of the unknown versus background category (p=0.600).

Similarly, in the greater than 0.6 to 4.0 μg/dl differential cortisol-response stratum, there were only two Ranch Hands with abnormalities: one in the low current dioxin category and one in the high current dioxin category. Among the participants with a differential cortisol response greater then 4.0 μg/dl, there were only two Ranch Hands in the unknown category with abnormal results of the funduscopic examination. Due to the sparse number of abnormalities in these strata, relative risks, confidence intervals, and most p-values were not presented.

After deletion of the categorized current dioxin-by-differential cortisol response interaction, the results of the adjusted analysis of the funduscopic examination were nonsignificant (Table 12-19 [f]: p>0.45 for each contrast).

Carotid Bruits

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal and maximal assumptions, the unadjusted and adjusted analyses revealed nonsignificant negative associations between initial dioxin and carotid bruits (Table 12-20 [a-d]: p>0.35 for each analysis).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of carotid bruits under both assumptions, only one Ranch Hand with 18.6 years or less since tour was diagnosed with carotid bruits (minimal: low current dioxin; maximal: medium current dioxin). The negative associations between current dioxin and carotid bruits were nonsignificant within the greater than 18.6 years time stratum of both the minimal and maximal cohorts (Table 12-20 [e] and [f]: p=0.315 and p=0.240). Due to the rarity of carotid bruits, adjusted analyses were not performed.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the prevalence of carotid bruits did not detect a significant overall difference among the four current dioxin categories (Table 12-20 [g]: p=0.236).

TABLE 12-20.

Analysis of Carotid Bruits

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=446)	Low	110	0.9	0.63 (0.21,1.85)	0.357
	Medium	224	1.3		
	High	112	0.0		
b) Maximal (n=647)	Low	173	0.6	0.81 (0.42,1.58)	0.517
	Medium	320	1.6		
	High	154	0.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=440)	0.62 (0.16,2.45)	0.446	AGE (p=0.017) DRKYR (p=0.034) HRTDIS (p=0.091)
d) Maximal (n=638)	0.86 (0.39,1.86)	0.686	AGE (p=0.001) DRKYR (p=0.040)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-20. (Continued)

Analysis of Carotid Bruits

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=446)	≤18.6	1.7 (59)	0.0 (113)	0.0 (46)	--	--
	>18.6	2.0 (49)	1.7 (115)	0.0 (64)	0.48 (0.12,2.00)	0.315[b]
f) Maximal (n=647)	≤18.6	0.0 (103)	0.6 (167)	0.0 (68)	--	--
	>18.6	2.9 (68)	2.0 (154)	0.0 (87)	0.60 (0.25,1.41)	0.240[b]

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

[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-20. (Continued)

Analysis of Carotid Bruits

g) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	703	0.6	All Categories		0.236
Unknown	320	1.6	Unknown vs. Background	2.77 (0.74,10.39)	0.228
Low	177	1.1	Low vs. Background	2.00 (0.36,10.99)	0.694
High	155	0.0	High vs. Background	–	0.900
Total	1,355				

h) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	703	All Categories		0.234	AGE (p=0.062)
Unknown	320	Unknown vs. Background	2.75 (0.73,10.36)	0.134	
Low	177	Low vs. Background	2.12 (0.38,11.74)	0.389	
High	155	High vs. Background	–	–	
Total	1,355				

--: Relative risk/confidence interval/p-value not presented due to the sparse number of abnormalities.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Adjustment for age did not change the lack of significance of the unadjusted analysis (Table 12-20 [h]: p=0.234).

Radial Pulses

In the minimal cohort, only one Ranch Hand had an abnormal (absent) radial pulse; he was in the low initial dioxin category. In the maximal cohort, there were two Ranch Hands with absent radial pulses: one in the low initial dioxin category and the other in the medium category. Due to this sparse number of abnormalities, relative risks, confidence intervals, and p-values were not presented for the initial dioxin or current dioxin and time since tour analyses. Similarly, only four Comparisons in the background category and one Ranch Hand in the unknown category had absent radial pulses. Thus, relative risks, confidence intervals, and p-values were not displayed for the analysis of categorized current dioxin. Table 12-21 presents the sample sizes and relative frequencies for all three analyses.

Femoral Pulses

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, the association between initial dioxin and femoral pulses was not significant under the minimal or the maximal assumption (Table 12-22 [a] and [b]: p=0.703 and p=0.922).

The adjusted analysis of the minimal and the maximal cohorts revealed significant interactions between initial dioxin and personality type (Table 12-22 [c] and [d]: p=0.027 and p=0.032, respectively). Stratified analyses of these interactions displayed a significant positive association between initial dioxin and absent femoral pulses for type A Ranch Hands (Appendix Table K-1: minimal assumption, Adj. RR=3.28, p=0.045; maximal assumption, Adj. RR=3.09, p=0.038). In contrast, the analyses of type B Ranch Hands exhibited nonsignificant negative associations between initial dioxin and abnormal femoral pulses (minimal assumption, Adj. RR=0.65, p=0.319; maximal assumption, Adj. RR=0.86, p=0.604). However, of the type A Ranch Hands in both the minimal and maximal cohorts, only two (both in the high initial dioxin category) had absent femoral pulses. Thus, the stratified analyses may have been affected by this sparse number of abnormalities.

After deletion of the initial dioxin-by-personality type interactions, neither the minimal nor the maximal adjusted analysis detected a significant association between initial dioxin and the frequency of Ranch Hands with abnormal femoral pulses (Table 12-22 [c] and [d]: p=0.984 and p=0.683, respectively).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal and the maximal assumptions, the unadjusted analyses of femoral pulses did not detect a significant interaction between current dioxin and time since tour (Table 12-22 [e] and [f]: p=0.562 and p=0.656, respectively). The associations between current dioxin and the femoral pulses were also nonsignificant within each time stratum for the minimal and maximal cohorts.

TABLE 12-21.

Analysis of Radial Pulses

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	n	Percent Abnormal
a) Minimal (n=442)	Low	109	0.9
	Medium	223	0.0
	High	110	0.0
b) Maximal (n=641)	Low	172	0.6
	Medium	318	0.3
	High	151	0.0

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin		
		Low	Medium	High
c) Minimal (n=442)	≤18.6	0.0 (58)	0.0 (113)	0.0 (46)
	>18.6	2.0 (49)	0.0 (114)	0.0 (62)
d) Maximal (n=641)	≤18.6	1.0 (102)	0.0 (166)	0.0 (68)
	>18.6	0.0 (68)	0.7 (152)	0.0 (85)

Note: Initial Dioxin: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

Current Dioxin: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-21. (Continued)

Analysis of Radial Pulses

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	n	Percent Yes
Background	694	0.6
Unknown	317	0.3
Low	176	0.0
High	153	0.0
Total	1,340	

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 12-22.

Analysis of Femoral Pulses

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=442)	Low	109	0.0	0.90 (0.51,1.59)	0.703
	Medium	223	3.6		
	High	110	1.8		
b) Maximal (n=641)	Low	172	1.2	1.02 (0.68,1.53)	0.922
	Medium	318	2.8		
	High	151	1.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=425)	1.01 (0.55,1.86)**	0.984**	INIT*PERS (p=0.027) AGE (p=0.004) CHOL (p=0.078) DIFCORT (p=0.041) HRTDIS (p=0.078)
d) Maximal (n=615)	1.11 (0.69,1.78)**	0.683**	INIT*PERS (p=0.032) AGE (p=0.003) PACKYR (p=0.024) CHOL (p=0.038) %BFAT (p=0.109) HRTDIS (p=0.113)

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

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-22. (Continued)

Analysis of Femoral Pulses

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=442)						0.562[b]
	≤18.6	0.0 (58)	2.7 (113)	0.0 (46)	0.96 (0.32,2.93)	0.950[c]
	>18.6	6.1 (49)	2.6 (114)	1.6 (62)	0.64 (0.29,1.42)	0.271[c]
f) Maximal (n=641)						0.656[b]
	≤18.6	1.0 (102)	1.2 (166)	1.5 (68)	1.05 (0.48,2.30)	0.906[c]
	>18.6	2.9 (68)	3.3 (152)	2.4 (85)	0.84 (0.50,1.43)	0.527[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=425)			0.407[b]	AGE (p=0.020)
	≤18.6	1.33 (0.41,4.30)	0.634[c]	CHOL (p=0.092)
	>18.6	0.71 (0.30,1.67)	0.429[c]	PERS (p=0.136)
				DIFCORT (p=0.057)
				HRTDIS (p=0.082)
h) Maximal (n=613)			****	CURR*TIME*%BFAT
	≤18.6	****	****	(p<0.001)
	>18.6	****	****	CURR*TIME*DIFCORT
				(p=0.005)
				AGE (p=0.004)
				PACKYR (p=0.025)
				CHOL (p=0.012)
				PERS (p=0.017)
				HRTDIS (p=0.032)

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

****Log_2 (current dioxin)-by-time-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-22. (Continued)

Analysis of Femoral Pulses

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	694	0.7	All Categories		0.227
Unknown	317	1.9	Unknown vs. Background	2.66 (0.81,8.78)	0.187
Low	176	2.3	Low vs. Background	3.21 (0.85,12.06)	0.175
High	153	2.0	High vs. Background	2.76 (0.65,11.66)	0.322
Total	1,340				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	660	All Categories		0.141**	DXCAT*PERS (p=0.030)
Unknown	300	Unknown vs. Background	2.43 (0.69,8.57)**	0.169**	AGE (p=0.001)
Low	172	Low vs. Background	3.48 (0.91,13.38)**	0.070**	
High	148	High vs. Background	4.52 (1.00,20.31)**	0.049**	
Total	1,280				

**Categorized current dioxin-by-covariate interation ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

The adjustment for covariate information did not change the lack of significance of the minimal analysis of femoral pulses with current dioxin and time since tour (Table 12-22 [g]: $p>0.40$ for interaction and time-specific analyses). However, under the maximal assumption, the adjusted analysis of femoral pulses detected significant interactions among current dioxin, time, and percent body fat and among current dioxin, time, and differential cortisol response (Table 12-22 [h]: $p<0.001$ and $p=0.005$). Stratified analyses were performed for each percent body fat-by-differential cortisol-response stratum (Appendix Table K-1). The absence of femoral pulses was relatively rare in the 12 time and covariate strata. Only four Ranch Hands (all having normal percent body fat) with later tours had an abnormal femoral pulse; three had a differential cortisol response of 0.6 μg/dl or less (two with medium current dioxin and one with high current dioxin) and the other Ranch Hand had greater than 4.0 μg/dl (low current dioxin). The remaining nine Ranch Hands with earlier tours and abnormal femoral pulses were scattered throughout the six covariate strata (see Appendix Table K-1). These interactions were most likely affected by the sparseness of Ranch Hands who had absent femoral pulses.

Results of Analyses Without Adjustment for Cholesterol and Percent Body Fat. After removing cholesterol and percent body fat from the maximal adjusted analysis of femoral pulses, the current dioxin-by-time-by-differential cortisol interaction was no longer significant. The adjusted analysis after the above exclusions did not detect any significant results (Appendix Table K-2: $p\geq0.60$ for the interaction and time-specific analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis did not detect any significant differences among the frequencies of absent femoral pulses of the four current dioxin categories (Table 12-22 [i]: $p>0.15$ for each contrast). Ranch Hands in all three current dioxin categories (unknown, low, and high) had a nonsignificant but higher risk of abnormal femoral pulses than the Comparisons in the background category.

The adjusted analysis of femoral pulses revealed a significant interaction between categorized current dioxin and personality type (Table 12-22 [j]: $p=0.030$). Appendix Table K-1 presents stratified analyses for this interaction. Only two type A participants (both Ranch Hands in the high current dioxin category) had absent femoral pulses; the contrast of the Ranch Hands in the high category versus the Comparisons in the background category was marginally significant ($p=0.066$). For type B participants, the overall contrast of the four current dioxin categories was not significant ($p=0.296$). However, the Ranch Hands in the low category had a marginally higher risk of an absent femoral pulse relative to the Comparisons in the background category (Adj. RR=3.47, 95% C.I.: [0.90,13.39], $p=0.071$). The relative frequencies of participants with absent femoral pulses were 1.3, 3.3, 4.1, and 1.2 percent for the background, unknown, low, and high current dioxin categories.

After deletion of the categorized current dioxin-by-personality type interaction from the model and adjusting only for age and personality type, the simultaneous contrast of the frequencies of abnormal femoral pulses of the four current dioxin categories remained nonsignificant (Table 12-22 [j]: $p=0.141$). However, similar to the analysis of type B participants in the stratified analyses, the contrast of the frequency of Ranch Hands having abnormal femoral pulses in the low category was marginally higher than the corresponding frequency of Comparisons in the background category (Adj. RR=3.48, 95% C.I.: [0.91,13.38],

p=0.070). Also, Ranch Hands in the high current dioxin category had a significantly higher risk of an absent femoral pulse than the Comparisons in the background category (Adj. RR=4.52, 95% C.I.: [1.00,20.31], p=0.049). The relative frequencies of participants with abnormal femoral pulses were 0.7, 1.9, 2.3, and 2.0 percent for the background, unknown, low, and high current dioxin categories. These results may have been affected by the sparse number of abnormalities.

Popliteal Pulses

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analysis under the minimal and maximal assumptions displayed a nonsignificant association between initial dioxin and the frequency of Ranch Hands with absent popliteal pulses (Table 12-23 [a] and [b]: p=0.124 and p=0.802, respectively).

After adjustment for covariate information, the results of the minimal and maximal analyses remained nonsignificant (Table 12-23 [c] and [d]: p=0.230 and p=0.865, respectively).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal and the maximal assumptions, the unadjusted analyses of popliteal pulses detected nonsignificant interactions between current dioxin and time since tour (Table 12-23 [e] and [f]: p=0.762 and p=0.881, respectively). The associations between current dioxin and popliteal pulses were also negative and nonsignificant within all time strata.

The minimal adjusted analysis revealed a significant current dioxin-by-time-by-family history of heart disease interaction (Table 12-23 [g]: p=0.034). To examine this interaction, Appendix K-1 presents stratified analyses for Ranch Hands with and without a family history of heart disease. Of the participants with a family history of heart disease, only one Ranch Hand with a later tour (low current dioxin) and one Ranch Hand with an earlier tour (medium current dioxin) had an absent popliteal pulse. In addition, for Ranch Hands without a family history of heart disease, the negative associations between current dioxin and the prevalence of absent popliteal pulse did not differ significantly between time strata and were nonsignificant (p>0.20 for the interaction and time-specific analyses). After deletion of this interaction, the minimal adjusted analysis exhibited a nonsignificant current dioxin-by-time since tour interaction (Table 12-23 [g]: p=0.723) as well as nonsignificant negative associations between current dioxin and the frequency of Ranch Hands having abnormal popliteal pulses with each time stratum.

Under the maximal assumption, the adjusted analysis revealed a significant interaction among current dioxin, time, and lifetime cigarette smoking history (Table 12-23 [h]: p=0.035). To investigate this interaction, stratified analyses were performed for each lifetime cigarette smoking history stratum. In the nonsmoking stratum, only one Ranch Hand ($\leq$18.6 years since tour, low current dioxin category) had an absent popliteal pulse. Therefore, relative risks, confidence intervals, and p-values were not presented for this stratum.

TABLE 12-23.

Analysis of Popliteal Pulses

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=442)	Low	109	2.8	0.67 (0.39,1.16)	0.124
	Medium	223	4.9		
	High	110	0.9		
b) Maximal (n=641)	Low	172	1.2	0.96 (0.67,1.37)	0.802
	Medium	318	4.4		
	High	151	1.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=427)	0.72 (0.40,1.28)	0.230	AGE (p=0.024) PERS (p=0.023) DIFCORT (p=0.010)
d) Maximal (n=620)	1.03 (0.71,1.51)	0.865	AGE (p=0.012) DIFCORT (p=0.059)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-23. (Continued)

Analysis of Popliteal Pulses

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=442)						0.762[b]
	≤18.6	3.5 (58)	3.5 (113)	0.0 (46)	0.50 (0.17,1.49)	0.211[c]
	>18.6	4.1 (49)	6.1 (114)	0.0 (62)	0.61 (0.29,1.25)	0.178[c]
f) Maximal (n=641)						0.881[b]
	≤18.6	1.0 (102)	3.0 (166)	1.5 (68)	0.91 (0.48,1.72)	0.776[c]
	>18.6	2.9 (68)	4.6 (152)	2.4 (85)	0.86 (0.53,1.38)	0.525[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=427)			0.723**[b]	CURR*TIME*HRTDIS (p=0.034)
	≤18.6	0.52 (0.15,1.86)**	0.317**[c]	AGE (p=0.038)
	>18.6	0.68 (0.33,1.42)**	0.303**[c]	PERS (p=0.018)
				DIFCORT (p=0.019)
h) Maximal (n=616)			0.880**[b]	CURR*TIME*PACKYR (p=0.035)
	≤18.6	0.94 (0.46,1.95)**	0.874**[c]	AGE (p=0.034)
	>18.6	0.88 (0.53,1.47)**	0.630**[c]	RACE (p=0.148)
				PERS (p=0.008)
				DIFCORT (p=0.049)

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-23. (Continued)

Analysis of Popliteal Pulses

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	694	2.0	All Categories		0.471
Unknown	317	2.2	Unknown vs. Background	1.10 (0.44,2.74)	0.999
Low	176	4.0	Low vs. Background	2.01 (0.80,5.06)	0.222
High	153	2.0	High vs. Background	0.97 (0.28,3.42)	0.999
Total	1,340				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	660	All Categories		0.490	AGE (p=0.001) PACKYR (p=0.049)
Unknown	300	Unknown vs. Background	0.98 (0.37,2.62)	0.973	PERS (p=0.026)
Low	172	Low vs. Background	2.07 (0.80,5.35)	0.133	
High	148	High vs. Background	1.49 (0.41,5.45)	0.548	
Total	1,280				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

The interaction between current dioxin and time since tour was nonsignificant in the analyses of moderate and heavy smokers (Appendix Table K-1: >0-10 pack-years, p=0.625; >10 pack-years, p=0.120). In the moderate smoking stratum, there was a nonsignificant negative relationship between current dioxin and the frequency of absent popliteal pulses for Ranch Hands with later tours and a nonsignificant positive association for Ranch Hands with early tours. In contrast, for the heavy-smoking stratum, there was a nonsignificant positive association between current dioxin and the prevalence of absent popliteal pulses for Ranch Hands with late tours and a nonsignificant negative association for Ranch Hands with early tours.

After deleting the current dioxin-by-time-by-lifetime cigarette smoking history interaction from the model, the maximal adjusted analysis displayed nonsignificant results consistent with the unadjusted analysis (Table 12-23 [h]: p>0.60 for the interaction and time-specific analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted and adjusted analyses of the prevalence of abnormal popliteal pulses, the simultaneous contrast of the four current dioxin categories was not significant (Table 12-23 [i] and [j]: p=0.471 and p=0.490, respectively). The Ranch Hands versus Comparisons contrasts were also nonsignificant.

Dorsalis Pedis Pulses

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Based on the minimal assumption, the unadjusted analysis displayed a nonsignificant positive association between initial dioxin and the prevalence of abnormal dorsalis pedis pulses (Table 12-24 [a]: p=0.322). However, the maximal unadjusted analysis of dorsalis pedis pulses detected a marginally significant positive association with initial dioxin (Table 12-24 [b]: Est. RR=1.16, p=0.089). The relative frequencies of Ranch Hands in the maximal cohort who had absent dorsalis pedis pulses were 9.4, 11.6, and 15.2 percent for the low, medium, and high initial dioxin categories.

The minimal adjusted analysis of dorsalis pedis pulses revealed a significant interaction between initial dioxin and differential cortisol response (Table 12-24 [c]: p=0.014). The stratified analyses found a nonsignificant negative association between initial dioxin and the prevalence of abnormal dorsalis pedis pulses for Ranch Hands with a differential cortisol response of 0.6 µg/dl or less (Appendix Table K-1: Adj. RR=0.90, p=0.578). In contrast, for Ranch Hands with a differential cortisol response between 0.6 µg/dl and 4.0 µg/dl, there was a marginally significant positive association between initial dioxin and dorsalis pedis pulses (Adj. RR=1.42, p=0.056) and a nonsignificant positive association for Ranch Hands with over 4.0 µg/dl (Adj. RR=1.55, p=0.207). In the moderate differential cortisol-response stratum, the frequencies of Ranch Hands with absent dorsalis pedis pulses increased steadily with increasing initial dioxin (low, 4.8%; medium, 11.3%; high, 20.0%).

After deletion of the interaction, the adjusted minimal analysis displayed a nonsignificant association between initial dioxin and the prevalence of abnormal dorsalis pedis pulses (Table 12-24 [c]: p=0.153). After adjustment for age and differential cortisol,

TABLE 12-24.

Analysis of Dorsalis Pedis Pulses

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=442)	Low	109	9.2	1.13 (0.89,1.42)	0.322
	Medium	223	13.5		
	High	110	15.5		
b) Maximal (n=640)	Low	171	9.4	1.16 (0.98,1.38)	0.089
	Medium	318	11.6		
	High	151	15.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=430)	1.20 (0.94,1.53)**	0.153**	INIT*DIFCORT (p=0.014) AGE (p=0.071)
d) Maximal (n=619)	1.21 (1.01,1.46)	0.041	AGE (p=0.010) DIFCORT (p=0.007)

[a]Relative risk for a twofold increase in dioxin.
**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-24. (Continued)

Analysis of Dorsalis Pedis Pulses

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=442)						0.273[b]
	≤18.6	10.3 (58)	10.6 (113)	15.2 (46)	1.27 (0.87,1.85)	0.208[c]
	>18.6	12.2 (49)	15.8 (114)	12.9 (62)	0.97 (0.70,1.33)	0.832[c]
f) Maximal (n=640)						0.497[b]
	≤18.6	7.9 (101)	10.8 (166)	14.7 (68)	1.21 (0.93,1.58)	0.155[c]
	>18.6	10.3 (68)	15.1 (152)	11.8 (85)	1.07 (0.85,1.36)	0.569[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=430)			0.129[b]	AGE (p=0.062)
	≤18.6	1.50 (1.00,2.24)	0.051[c]	DIFCORT (p=0.002)
	>18.6	1.01 (0.73,1.41)	0.941[c]	
h) Maximal (n=619)			0.355[b]	AGE (p=0.010)
	≤18.6	1.34 (1.00,1.78)	0.048[c]	DIFCORT (p=0.006)
	>18.6	1.12 (0.88,1.44)	0.355[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-24. (Continued)

Analysis of Dorsalis Pedis Pulses

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	694	9.4	All Categories		0.295
Unknown	316	11.1	Unknown vs. Background	1.21 (0.78,1.86)	0.399
Low	176	13.6	Low vs. Background	1.53 (0.93,2.52)	0.097
High	153	13.1	High vs. Background	1.46 (0.85,2.48)	0.169
Total	1,339				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	654	All Categories		0.146	AGE (p=0.003) CHOL (p=0.082)
Unknown	296	Unknown vs. Background	1.17 (0.74,1.86)	0.500	PERS (p=0.147)
Low	171	Low vs. Background	1.62 (0.97,2.70)	0.066	DIFCORT (p=0.138)
High	145	High vs. Background	1.72 (0.98,3.04)	0.061	
Total	1,266				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

the maximal analysis revealed a significant positive association between initial dioxin and the frequency of Ranch Hands having abnormal dorsalis pedis pulses (Table 12-24 [d]: Adj. RR=1.21, p=0.041).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal and the maximal assumptions, the unadjusted analyses of dorsalis pedis pulses displayed nonsignificant interactions between current dioxin and time since tour (Table 12-24 [e] and [f]: p=0.273 and p=0.497, respectively).

After including age and differential cortisol in the models of the minimal and maximal analyses, the interactions between current dioxin and time since tour remained nonsignificant (Table 12-24 [g] and [h]: p=0.129 and p=0.355, respectively). However, for Ranch Hands with later tours, there was a marginally significant positive association between current dioxin and the prevalence of abnormal dorsalis pedis pulses in the minimal cohort (Table 12-24 [g]: Adj. RR=1.50, p=0.051) and a significant positive association for this stratum of Ranch Hands in the maximal cohort (Table 12-24 [h]: Adj. RR=1.34, p=0.048). In the 18.6 years or less time stratum, the relative frequencies of Ranch Hands with absent dorsalis pedis pulses were 10.3, 10.6, and 15.2 percent for low, medium, and high current dioxin under the minimal assumption and 7.9, 10.8, and 14.7 percent for low, medium, and high current dioxin based on the maximal assumption.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of the prevalence of abnormal dorsalis pedis pulses, the simultaneous contrast of the four current dioxin categories was not significant (Table 12-24 [i]: p=0.295). However, the Ranch Hands in the low current dioxin category had a marginally higher risk of an absent dorsalis pedis pulse than the Comparisons in the background category (Adj. RR=1.53, 95% C.I.: [0.93,2.52], p=0.097). The percentages of participants with an abnormal dorsalis pedis pulse for the background, unknown, low, and high current dioxin categories were 9.4, 11.1, 13.6, and 13.1 percent.

After adjusting for age, cholesterol, personality type, and differential cortisol response in the analysis of dorsalis pedis pulses, the overall contrast of the four current dioxin categories remained nonsignificant (Table 12-24 [j]: p=0.146). The Ranch Hands in the low and high current dioxin categories had marginally higher risks of an absent dorsalis pedis pulse relative to the Comparisons in the background category (low vs. background: Adj. RR=1.62, 95% C.I.: [0.97,2.70], p=0.066; high vs. background: Adj. RR=1.72, 95% C.I.: [0.98,3.04], p=0.061).

Results of Analyses Without Adjustment for Cholesterol. After removing cholesterol from the adjusted analysis of dorsalis pedis pulses, the overall contrast of the four current dioxin categories became marginally significant (Appendix Table K-2: p=0.087). Also, the contrast of the Ranch Hands in the high current dioxin category versus the Comparisons in the background category became significant (Adj. RR=1.86, 95% C.I.: [1.07,3.26], p=0.029).

Posterior Tibial Pulses

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal and the maximal assumptions, the unadjusted analysis of the prevalence of absent posterior tibial pulses did not detect a significant association with initial dioxin (Table 12-25 [a] and [b]: p=0.333 and p=0.346, respectively).

The adjusted minimal analysis of the frequency of Ranch Hands having abnormal posterior tibial pulses and initial dioxin remained nonsignificant (Table 12-25 [c]: p=0.921). However, after adjusting for age, percent body fat, personality type, and differential cortisol response, the maximal analysis detected a marginally significant positive association between initial dioxin and the prevalence of absent posterior tibial pulses in Ranch Hands (Table 12-25 [d]: Adj. RR=1.38, p=0.086). Under the maximal assumption, there were no Ranch Hands in the low initial dioxin category who had abnormal posterior tibial pulses, but 4.7 and 2.7 percent of the Ranch Hands in the medium and high initial dioxin categories, respectively, had absent posterior tibial pulses.

Results of Analyses Without Adjustment for Percent Body Fat. After excluding percent body fat from the maximal adjusted model and adjusting only for age, personality type, and differential cortisol response, the positive association between initial dioxin and the prevalence of absent posterior tibial pulses in Ranch Hands became nonsignificant (Appendix Table K-2: Adj. RR=1.34, p=0.124).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal and the maximal assumptions, the unadjusted analysis of the frequency of abnormal posterior tibial pulses in Ranch Hands displayed nonsignificant interactions between current dioxin and time since tour (Table 12-25 [e] and [f]: p=0.756 and p=0.733, respectively). The associations between current dioxin and the prevalence of abnormal posterior tibial pulses were also nonsignificant within each time stratum of the minimal and maximal cohorts.

The adjusted minimal analysis of posterior tibial pulses with current dioxin and time since tour remained nonsignificant (Table 12-25 [g]: p>0.60 for the interaction and time-specific analyses). After adjusting the maximal analysis for age, percent body fat, and differential cortisol response, the interaction between current dioxin and time remained nonsignificant (Table 12-25 [h]: p=0.297). However, for Ranch Hands in the maximal cohort with 18.6 years or less since tour, there was a marginally significant positive association between current dioxin and the frequency of Ranch Hands with abnormal posterior tibial pulses (Adj. RR=1.88, p=0.087). In the maximal cohort, 4.2 percent of the Ranch Hands with medium current dioxin had an abnormal posterior tibial pulse, while none with low or high current dioxin were classified as abnormal.

Results of Analyses Without Adjustment for Percent Body Fat. After removing percent body fat from the maximal adjusted model, the positive association between current dioxin and abnormal posterior tibial pulses became nonsignificant for Ranch Hands with 18.6 years or less since tour (Appendix Table K-2: Adj. RR=1.65, p=0.146).

TABLE 12-25.

Analysis of Posterior Tibial Pulses

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=442)	Low	109	1.8	0.81 (0.51,1.27)	0.333
	Medium	223	6.3		
	High	110	1.8		
b) Maximal (n=640)	Low	171	0.0	1.17 (0.85,1.61)	0.346
	Medium	318	4.7		
	High	151	2.7		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=430)	1.02 (0.64,1.65)	0.921	AGE (p<0.001) %BFAT (p=0.033) DIFCORT (p<0.001)
d) Maximal (n=603)	1.38 (0.97,1.98)	0.086	AGE (p<0.001) %BFAT (p=0.058) PERS (p=0.136) DIFCORT (p<0.001)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-25. (Continued)

Analysis of Posterior Tibial Pulses

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.756[b]
(n=442)	≤18.6	1.7 (58)	5.3 (113)	0.0 (46)	0.60 (0.24,1.50)	0.273[c]
	>18.6	2.0 (49)	7.9 (114)	1.6 (62)	0.71 (0.39,1.30)	0.263[c]
f) Maximal						0.733[b]
(n=640)	≤18.6	0.0 (101)	4.2 (166)	0.0 (68)	1.15 (0.65,2.04)	0.636[c]
	>18.6	1.5 (68)	5.9 (152)	2.4 (85)	1.01 (0.67,1.54)	0.946[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.762[b]	AGE (p<0.001)
(n=430)	≤18.6	1.05 (0.35,3.15)	0.937[c]	%BFAT (p=0.033)
	>18.6	0.86 (0.47,1.59)	0.629[c]	DIFCORT (p<0.001)
h) Maximal			0.297[b]	AGE (p<0.001)
(n=619)	≤18.6	1.88 (0.91,3.88)	0.087[c]	%BFAT (p=0.036)
	>18.6	1.20 (0.77,1.86)	0.413[c]	DIFCORT (p<0.001)

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-25. (Continued)

Analysis of Posterior Tibial Pulses

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	694	2.2	All Categories		<0.001
Unknown	316	1.0	Unknown vs. Background	0.43 (0.12,1.51)	0.270
Low	176	7.4	Low vs. Background	3.61 (1.68,7.74)	0.003
High	153	1.3	High vs. Background	0.60 (0.14,2.65)	0.764
Total	1,339				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	694	All Categories		<0.001	AGE (p<0.001)
Unknown	316	Unknown vs. Background	0.38 (0.11,1.34)	0.131	%BFAT (p=0.055)
Low	176	Low vs. Background	4.46 (2.02,9.82)	<0.001	
High	153	High vs. Background	1.12 (0.25,5.14)	0.880	
Total	1,339				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In both the unadjusted and adjusted analyses of abnormal posterior tibial pulses, the simultaneous contrasts of the four current dioxin categories were significant (Table 12-25 [i] and [j]: $p<0.001$ for each analysis). Also, for both analyses, Ranch Hands in the low current dioxin category had a higher risk of abnormal posterior tibial pulses than the Comparisons in the background category (unadjusted: Est. RR=3.61, 95% C.I.: [1.68,7.74], p=0.003; adjusted: Adj. RR=4.46, 95% C.I.: [2.02, 9.82], $p<0.001$). The relative frequencies of participants with absent posterior tibial pulses were 2.2, 1.0, 7.4, and 1.3 percent for the background, unknown, low, and high current dioxin categories.

Leg Pulses

The primary analyses for leg pulses excluded diabetics. However, additional analyses (unadjusted and adjusted for age) were done based on diabetics only. Appendix Table K-5 details the results of these analyses. There were no significant results found in these analyses. The unadjusted categorized current dioxin analysis showed a marginally significant increased risk of leg pulses for diabetic Ranch Hands in the low current dioxin category relative to diabetic Comparisons in the background category (Est. RR=3.34, 95% C.I.: [0.95,11.59], p=0.057), but this contrast became nonsignificant after adjustment for age (Adj. RR=2.76, 95% C.I.: [0.76,9.94], p=0.119). The prevalences of leg pulse abnormalities based on diabetics only were 18.3, 16.7, 42.9, and 17.9 percent for the background, unknown, low, and high current dioxin categories.

The following discussion of the leg pulse analyses is based on participants who were not classified as diabetic.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the analysis of abnormal leg pulses and initial dioxin was nonsignificant (Table 12-26 [a]: p=0.636). Based on the maximal assumption, there was a marginally significant positive association between initial dioxin and the prevalence of abnormal leg pulses in Ranch Hands (Table 12-26 [b]: Est. RR=1.15, p=0.085). The relative frequencies of Ranch Hands in the maximal cohort with abnormal leg pulses became larger with increasing levels of initial dioxin (low, 10.5%; medium, 15.1%; high, 17.9%).

The minimal adjusted analysis of leg pulses revealed a significant interaction between initial dioxin and age (Table 12-26 [c]: p=0.017). The stratified analyses (Appendix Table K-1) exhibited a nonsignificant negative association between initial dioxin and absent leg pulses for the younger Ranch Hands (Adj. RR=0.86, p=0.396) and a significant positive association for the older Ranch Hands (Adj. RR=1.41, p=0.030). The relative frequencies of older Ranch Hands with abnormal leg pulses in the low, medium, and high initial dioxin categories were 8.8, 25.0, and 27.8 percent.

After deletion of the initial dioxin-by-age interaction, the minimal analysis of initial dioxin and leg pulses was nonsignificant (Table 12-26 [c]: p=0.289). Under the maximal assumption, the adjustment for age and differential cortisol response caused the positive association between initial dioxin and the frequency of absent leg pulses to become significant (Table 12-26 [d]: Adj. RR=1.22, p=0.021).

TABLE 12-26.

Analysis of Leg Pulses

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=442)	Low	109	11.9	1.05 (0.85,1.31)	0.636
	Medium	223	17.9		
	High	110	17.3		
b) Maximal (n=640)	Low	171	10.5	1.15 (0.98,1.35)	0.085
	Medium	318	15.1		
	High	151	17.9		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=430)	1.13 (0.90,1.42)**	0.289**	INIT*AGE (p=0.017) %BFAT (p=0.086) DIFCORT (p=0.025)
d) Maximal (n=619)	1.22 (1.03,1.45)	0.021	AGE (p<0.001) DIFCORT (p=0.040)

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

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-26. (Continued)

Analysis of Leg Pulses

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.369[b]
(n=442)	≤18.6	12.1 (58)	14.2 (113)	15.2 (46)	1.13 (0.79,1.61)	0.513[c]
	>18.6	16.3 (49)	21.1 (114)	16.1 (62)	0.91 (0.68,1.22)	0.533[c]
f) Maximal						0.609[b]
(n=640)	≤18.6	8.9 (101)	13.9 (166)	14.7 (68)	1.16 (0.91,1.50)	0.236[c]
	>18.6	11.8 (68)	19.7 (152)	15.3 (85)	1.07 (0.86,1.32)	0.550[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.220**[b]	CURR*TIME*PACKYR
(n=430)	≤18.6	1.31 (0.89,1.91)**	0.167**[c]	(p=0.031)
	>18.6	0.97 (0.72,1.32)**	0.866**[c]	AGE (p=0.005)
				%BFAT (p=0.147)
				DIFCORT (p=0.018)
h) Maximal			0.460[b]	AGE (p<0.001)
(n=619)	≤18.6	1.30 (0.99,1.71)	0.057[c]	DIFCORT (p=0.035)
	>18.6	1.14 (0.91,1.43)	0.239[c]	

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-26. (Continued)

Analysis of Leg Pulses

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	694	11.4	All Categories		0.077
Unknown	316	12.7	Unknown vs. Background	1.13 (0.75,1.69)	0.560
Low	176	18.8	Low vs. Background	1.80 (1.15,2.80)	0.010
High	153	15.0	High vs. Background	1.38 (0.83,2.27)	0.211
Total	1,339				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	656	All Categories		0.020	AGE (p<0.001)
Unknown	298	Unknown vs. Background	1.06 (0.69,1.62)	0.798	CHOL (p=0.122)
Low	171	Low vs. Background	1.92 (1.22,3.03)	0.005	PERS (p=0.119)
High	147	High vs. Background	1.71 (1.01,2.91)	0.047	
Total	1,272				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal and the maximal assumptions, the associations between current dioxin and absent leg pulses did not differ significantly between time since tour strata in the unadjusted analysis (Table 12-26 [e] and [f]: p=0.369 and p=0.609, respectively). These associations between current dioxin and leg pulses were also nonsignificant for each time stratum of the unadjusted analysis.

The adjusted minimal analysis of the prevalence of abnormal leg pulses revealed a significant interaction among current dioxin, time since tour, and lifetime cigarette smoking history (Table 12-26 [g]: p=0.031). In order to investigate this interaction, stratified analyses are presented in Appendix Table K-1 for each lifetime cigarette smoking history and time stratum. In the nonsmoking stratum, the interaction between current dioxin and time was not significant (p=0.159), nor were the associations between current dioxin and absent leg pulses within the time strata (≤18.6 years: Adj. RR=0.51, p=0.175; >18.6 years: Adj. RR=1.14, p=0.733).

Similarly, for Ranch Hands who were moderate smokers, the nonsignificant positive associations between current dioxin and abnormal leg pulses did not differ significantly between time strata (Appendix Table K-1: p>0.10 for the interaction and time-specific analyses). However, for heavy smokers, the interaction between current dioxin and time since tour was significant (p=0.003). The positive association between current dioxin and the prevalence of abnormal leg pulses was also significant for Ranch Hands with later tours (Adj. RR=2.73, p=0.008). The relative frequencies of Ranch Hands in this stratum with leg pulses classified as abnormal were 18.4 and 14.3 percent for medium and high current dioxin and 0.0 percent for low current dioxin. For Ranch Hands with earlier tours, the analysis detected a nonsignificant negative association between current dioxin and abnormal leg pulses (Adj. RR=0.75, p=0.231).

After deletion of the current dioxin-by-time-by-lifetime cigarette smoking history interaction, the minimal adjusted analysis of the prevalence of abnormal leg pulses was nonsignificant (Table 12-26 [g]: p>0.15 for the interaction and time-specific analyses).

In the maximal analysis of leg pulses, the adjustment for age and differential cortisol response did not alter the lack of significance of the interaction between current dioxin and time since tour (Table 12-26 [h]: p=0.460). However, within the 18.6 years or less time stratum, the positive association between current dioxin and abnormal leg pulses became marginally significant (Adj. RR=1.30, p=0.057). In the maximal cohort, the percentages of Ranch Hands with later tours who had abnormal leg pulses were 8.9, 13.9, and 14.7 percent for low, medium, and high current dioxin.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the prevalence of absent leg pulses detected a marginally significant difference among the four current dioxin categories (Table 12-26 [i]: p=0.077). Specifically, the Ranch Hands in the low current dioxin category had a significantly higher risk of abnormal leg pulses than the Comparisons in the background category (Est. RR=1.80, 95% C.I.: [1.15,2.80], p=0.010). Even though the low versus background contrast was the only significant contrast, the Ranch Hands in all three current dioxin categories had higher

percentages of absent leg pulses than the Comparisons in the background category (background, 11.4%; unknown, 12.7%; low, 18.8%; high, 15.0%).

After adjusting for age, cholesterol, and personality type, the overall contrast of the four current dioxin categories became significant in the analysis of leg pulses (Table 12-26 [j]: p=0.020). The contrast of the Ranch Hands in the low current dioxin category versus the Comparisons in the background category remained significant (Adj. RR=1.92, 95% C.I.: [1.22,3.03], p=0.005). Also, the contrast of the Ranch Hands in the high category versus the Comparisons in the background category became significant with the Ranch Hands having a greater risk of abnormal leg pulses than the Comparisons (Adj. RR=1.71, 95% C.I.: [1.01,2.91], p=0.047). The risk of absent leg pulses remained nonsignificantly higher for the Ranch Hands in the low category relative to the Comparisons in the background category (p=0.798).

Peripheral and All Pulses

The index of all pulses included the peripheral pulse index and the carotid pulse. These indices differed in the number of abnormalities only in the categorized current dioxin analyses, and, therefore, displayed equivalent results for the initial dioxin and current dioxin with time since tour analyses.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analyses of peripheral and all pulses displayed positive associations with initial dioxin that were nonsignificant for the minimal cohort (Table 12-27 [a]: Est. RR=1.04, p=0.718) and marginally significant for the maximal cohort (Table 12-27 [b]: Est. RR=1.15, p=0.092). The relative frequencies of Ranch Hands with abnormal peripheral and all pulses indices were 10.5, 15.4, and 17.9 percent for the low, medium, and high initial dioxin categories.

The adjusted minimal analysis of peripheral and all pulses revealed a significant interaction between initial dioxin and age (Table 12-27 [c]: p=0.013). In order to examine this interaction, stratified analyses were performed for the younger and older Ranch Hands (Appendix Table K-1). For the younger Ranch Hands, the stratified analyses exhibited a nonsignificant negative association between initial dioxin and age (Adj. RR=0.83, p=0.306). In contrast, the analysis of the older Ranch Hands found a significant positive association between initial dioxin and the prevalence of abnormal peripheral and all pulse indices (Adj. RR=1.41, p=0.029). The relative frequencies of the older Ranch Hands with abnormal peripheral and all pulse indices became larger with increasing levels of initial dioxin (low, 8.8%; medium, 25.0%; high, 27.8%).

After deletion of the initial dioxin-by-age interaction from the model, the minimal analysis of peripheral and all pulses was nonsignificant (Table 12-27 [c]: p=0.349). However, the adjustment for age and differential cortisol response caused the positive association between initial dioxin and the peripheral and all pulses indices to become significant under the maximal assumption (Table 12-27 [d]: Adj. RR=1.22, p=0.025).

TABLE 12-27.

Analysis of Peripheral and All Pulses

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=442)	Low	109	12.8	1.04 (0.84,1.29)	0.718
	Medium	223	17.9		
	High	110	17.3		
b) Maximal (n=640)	Low	171	10.5	1.15 (0.98,1.34)	0.092
	Medium	318	15.4		
	High	151	17.9		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=430)	1.12 (0.89,1.40)**	0.349**	INIT*AGE (p=0.013) %BFAT (p=0.140) DIFCORT (p=0.024)
d) Maximal (n=619)	1.22 (1.03,1.44)	0.025	AGE (p<0.001) DIFCORT (p=0.037)

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

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 12-27. (Continued)

Analysis of Peripheral and All Pulses

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.321[b]
(n=442)	≤18.6	12.1 (58)	14.2 (113)	15.2 (46)	1.13 (0.79,1.61)	0.513[c]
	>18.6	18.4 (49)	21.1 (114)	16.1 (62)	0.89 (0.67,1.19)	0.439[c]
f) Maximal						0.577[b]
(n=640)	≤18.6	8.9 (101)	13.9 (166)	14.7 (68)	1.16 (0.91,1.50)	0.236[c]
	>18.6	11.8 (68)	20.4 (152)	15.3 (85)	1.06 (0.86,1.31)	0.596[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.172**[b]	CURR*TIME*PACKYR
(n=430)	≤18.6	1.33 (0.91,1.95)**	0.136**[c]	(p=0.041)
	>18.6	0.96 (0.71,1.29)**	0.790**[c]	AGE (p=0.005) DIFCORT (p=0.016)
h) Maximal			0.436[b]	AGE (p=0.001)
(n=619)	≤18.6	1.30 (0.99,1.70)	0.062[c]	DIFCORT (p=0.032)
	>18.6	1.13 (0.90,1.42)	0.285[c]	

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 12-27. (Continued)

Analysis of Peripheral Pulses

i1) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	694	11.8	All Categories		0.113
Unknown	316	12.7	Unknown vs. Background	1.08 (0.72,1.62)	0.703
Low	176	18.8	Low vs. Background	1.72 (1.11,2.68)	0.016
High	153	15.0	High vs. Background	1.32 (0.80,2.18)	0.276
Total	1,339				

j1) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	660	All Categories		0.017	AGE (p<0.001) PERS (p=0.114)
Unknown	299	Unknown vs. Background	1.01 (0.66,1.55)	0.963	
Low	172	Low vs. Background	1.87 (1.18,2.94)	0.007	
High	148	High vs. Background	1.76 (1.05,2.97)	0.033	
Total	1,279				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 12-27. (Continued)

Analysis of All Pulses

i2) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	694	12.0	All Categories		0.133
Unknown	316	13.0	Unknown vs. Background	1.10 (0.74,1.64)	0.649
Low	176	18.8	Low vs. Background	1.70 (1.09,2.64)	0.019
High	153	15.0	High vs. Background	1.30 (0.79,2.15)	0.300
Total	1,339				

j2) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	660	All Categories		0.021	AGE (p<0.001) PERS (p=0.124)
Unknown	299	Unknown vs. Background	1.03 (0.67,1.56)	0.904	
Low	172	Low vs. Background	1.84 (1.17,2.90)	0.008	
High	148	High vs. Background	1.75 (1.04,2.95)	0.035	
Total	1,279				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal and the maximal assumptions, the associations between current dioxin and the prevalence of abnormal peripheral and all pulses indices did not differ significantly between the two time since tour strata (Table 12-27 [e] and [f]: p=0.321 and p=0.577, respectively).

The minimal adjusted analysis detected a significant interaction among current dioxin, time since tour, and lifetime cigarette smoking history (Table 12-27 [g]: p=0.041). Stratified analyses displayed nonsignificant current dioxin-by-time interactions for nonsmokers and moderate smokers (Appendix Table K-1: p=0.295 and p=0.807, respectively). These analyses also showed nonsignificant negative associations between current dioxin and the peripheral and all pulses indices within both time strata for Ranch Hands who did not smoke and nonsignificant positive associations within both time strata for Ranch Hands who smoked moderately.

In contrast, for Ranch Hands who were heavy smokers (>10 pack-years), the interaction between current dioxin and time was significant (Appendix Table K-1: p=0.003). The analysis of Ranch Hands with later tours revealed a significant positive association between current dioxin and the peripheral and all pulses indices (Adj. RR=2.71, p=0.008). For Ranch Hands with earlier tours, the stratified analysis exhibited a nonsignificant negative association with current dioxin (Adj. RR=0.75, p=0.237). The relative frequencies of abnormal peripheral and all pulses indices for Ranch Hands with later tours were 18.4 and 14.3 percent for medium and high current dioxin. There were no Ranch Hands with abnormal peripheral and all pulses indices and low current dioxin.

After deletion of the current dioxin-by-time-by-lifetime cigarette smoking history interaction, the minimal analysis of peripheral and all pulses was not significant (Table 12-27 [g]: p>0.10 for the interaction and time-specific analyses). After adjusting for age and differential cortisol response, the interaction between current dioxin and time since tour remained nonsignificant in the maximal analysis (Table 12-27 [h]: p=0.436). However, there was a marginally significant positive association between current dioxin and the peripheral and all pulses indices for Ranch Hands with 18.6 years or less since tour (Adj. RR=1.30, p=0.062) and a nonsignificant positive association for Ranch Hands with more than 18.6 years since tour (Adj. RR=1.13, p=0.285). The percentages of Ranch Hands in the maximal cohort with later tours who had abnormal peripheral and all pulses indices were 8.9, 13.9, and 14.7 percent for low, medium, and high current dioxin.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

Peripheral Pulses. In the unadjusted analysis of peripheral pulses, the simultaneous contrast of the four current dioxin categories was not significant (Table 12-27 [i1]: p=0.113). However, the Ranch Hands in the low current dioxin category had a significantly higher risk of an abnormal peripheral pulses index than the Comparisons in the background category (Est. RR=1.72, 95% C.I.: [1.11,2.68], p=0.016). In fact, the three current dioxin categories consisting of Ranch Hands had higher percentages of abnormal peripheral pulses indices than the background category of Comparisons (background, 11.8%; unknown, 12.7%; low, 18.8%; high, 15.0%).

After adjusting for age and personality type, the analysis of peripheral pulses detected a significant difference among the four current dioxin categories (Table 12-27 [j1]: p=0.017). Similar to the unadjusted analysis, the Ranch Hands in the low current dioxin category had a significantly higher risk of abnormal peripheral pulses than the Comparisons in the background category (Adj. RR=1.87, 95% C.I.: [1.18,2.94], p=0.007). The Ranch Hands in the high current dioxin category also had a significantly higher risk of an abnormal peripheral pulses index than the Comparisons in the background category (Adj. RR=1.76, 95% C.I.: [1.05,2.97], p=0.033).

All Pulses. The unadjusted analysis of the all pulses index did not detect a significant overall difference among the four current dioxin categories (Table 12-27 [i2]: p=0.133). Similar to the analysis of the peripheral pulses index, the contrast of the Ranch Hands in the low current dioxin category versus the Comparisons in the background category was significant (Est. RR=1.70, 95% C.I.: [1.09,2.64], p=0.019). The relative frequencies of abnormal all pulses indices were 12.0, 13.0, 18.8, and 15.0 percent for the background, unknown, low, and high current dioxin categories.

The adjustment for age and personality type caused the analysis of all pulses to detect a significant simultaneous contrast of the four current dioxin categories (Table 12-27 [j2]: p=0.021). Also, similar to the analysis of peripheral pulses, Ranch Hands in both the low category and the high category had a significantly higher risk of an abnormal all pulses index than the Comparisons in the background category (low versus background: Adj. RR=1.84, 95% C.I.: [1.17,2.90], p=0.008; high versus background: Adj. RR=1.75, 95% C.I.: [1.04,2.95], p=0.035).

Longitudinal Analysis

Physical Examination Variable

Overall ECG

For the cardiovascular examination, longitudinal analyses were conducted to examine the percentage of participants having a normal ECG reading at the 1982 examination and an abnormal reading at the 1987 examination for associations with initial dioxin, current dioxin and time since tour, and categorized current dioxin. Table 12-28 presents the results of these analyses.

For a specific longitudinal analysis (e.g., minimal assumption, initial dioxin analysis), the upper part of each subpanel of a table provides the percentages of participants with an abnormal ECG at each examination. The lower part of each subpanel presents sample sizes, percentages, relative risks, and associated 95 percent confidence intervals subject to the requirement that participants were compliant at both the 1982 and 1987 examinations and had a normal ECG at the 1982 examination.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the longitudinal analyses of the minimal and maximal cohorts, the associations between the percentage of Ranch Hands having an abnormal ECG reading at the 1987 examination and initial dioxin were significant (Table 12-28 [a] and [b]: Est. RR=0.65,

TABLE 12-28.

Longitudinal Analysis of Overall Electrocardiograph (ECG)

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Percent Abnormal/(n) Examination 1982	1985	1987
a) Minimal	Low	23.1 (104)	17.5 (103)	16.4 (104)
	Medium	32.9 (216)	14.8 (210)	18.5 (216)
	High	22.4 (107)	10.4 (106)	13.1 (107)

Normal in 1982

Initial Dioxin	n in 1987	Percent Abnormal in 1987	Est. Relative Risk (95% C.I.)[a]	p-Value
Low	80	13.8	0.65 (0.44,0.94)	0.014
Medium	145	11.0		
High	83	6.0		

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 12-28. (Continued)

Longitudinal Analysis of Overall Electrocardiograph (ECG)

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Percent Abnormal/(n) Examination 1982	1985	1987
b) Maximal	Low	27.9 (158)	11.7 (154)	16.5 (158)
	Medium	28.1 (306)	14.4 (299)	17.7 (306)
	High	24.5 (147)	11.7 (145)	13.6 (147)

Normal in 1982

Initial Dioxin	n in 1987	Percent Abnormal in 1987	Est. Relative Risk (95% C.I.)[a]	p-Value
Low	114	12.3	0.78 (0.61,1.00)	0.041
Medium	220	13.2		
High	111	4.5		

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 12-28. (Continued)

Longitudinal Analysis of Overall Electrocardiograph (ECG)

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin Low	Medium	High
c) Minimal	≤18.6	1982	19.6 (56)	33.9 (109)	15.9 (44)
		1985	14.6 (55)	14.2 (106)	9.3 (43)
		1987	14.3 (56)	16.5 (109)	11.4 (44)
	>18.6	1982	23.9 (46)	32.4 (111)	27.9 (61)
		1985	20.0 (45)	14.7 (109)	13.1 (61)
		1987	21.7 (46)	18.0 (111)	16.4 (61)

Time (Yrs.)	Normal in 1982: Percent Abnormal/(n) in 1987 Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
					0.189[b]
≤18.6	11.1 (45)	9.7 (72)	5.4 (37)	0.81 (0.47,1.41)	0.460[c]
>18.6	22.9 (35)	9.3 (75)	6.8 (44)	0.48 (0.27,0.86)	0.013[c]

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 12-28. (Continued)

Longitudinal Analysis of Overall Electrocardiograph (ECG)

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin Low	Medium	High
d) Maximal	≤18.6	1982	25.3 (91)	28.1 (160)	20.0 (65)
		1985	11.4 (88)	12.8 (156)	10.9 (64)
		1987	15.4 (91)	15.0 (160)	12.3 (65)
	>18.6	1982	29.2 (65)	30.6 (147)	25.3 (83)
		1985	12.7 (63)	16.0 (144)	12.1 (83)
		1987	20.0 (65)	19.1 (147)	15.7 (83)

Time (Yrs.)	Normal in 1982: Percent Abnormal/(n) in 1987 Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
					0.281[b]
≤18.6	11.8 (68)	9.6 (115)	5.8 (52)	0.88 (0.61,1.27)	0.496[c]
>18.6	15.2 (46)	15.7 (102)	4.8 (62)	0.66 (0.46,0.95)	0.025[c]

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

TABLE 12-28. (Continued)

Longitudinal Analysis of Overall Electrocardiograph (ECG)

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Percent Abnormal/(n) Examination 1982	1985	1987
Background	27.7 (606)	13.0 (598)	19.0 (606)
Unknown	24.5 (290)	9.5 (283)	15.2 (290)
Low	36.3 (171)	15.1 (166)	18.1 (171)
High	23.0 (148)	11.6 (147)	14.2 (148)

Normal in 1982

Current Dioxin Category	n in 1987	Percent Abnormal in 1987	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	438	10.5	All Categories		0.224
Unknown	219	11.9	Unknown vs. Background	1.15 (0.69,1.91)	0.597
Low	109	11.0	Low vs. Background	1.05 (0.54,2.06)	0.878
High	114	5.3	High vs. Background	0.47 (0.20,1.14)	0.094

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.
Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results. Statistical analyses are based only on participants who were normal in 1982 (see Chapter 4, Statistical Methods).

p=0.014 and Est. RR=0.78, p=0.041, respectively). For the minimal cohort, the percentage of participants with an abnormal reading in 1987 (based on those with a normal ECG reading in 1982) decreased steadily with increasing current dioxin (low, 13.8%; medium, 11.0%; high, 6.0%). The corresponding percentages for the maximal cohort were 12.3, 13.2, and 4.5 percent for the low, medium, and high initial dioxin categories.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The longitudinal analysis of the 1987 ECG did not detect a significant current dioxin-by-time since tour interaction for the minimal cohort (Table 12-28 [c]: p=0.189). Thus, the association with current dioxin did not differ for the two time strata. However, there was a significant negative association between current dioxin and the overall ECG reading for Ranch Hands with more than 18.6 years since tour (Est. RR=0.48, p=0.013). The percentages of these Ranch Hands with an abnormal 1987 ECG reading (based on those with a normal ECG reading in 1982) were 22.9, 9.3, and 6.8 percent for low, medium, and high current dioxin.

Similarly, under the maximal assumption, the interaction between current dioxin and time since tour in the longitudinal analysis of the 1987 ECG was nonsignificant (Table 12-28 [d]: p=0.281). For Ranch Hands with more than 18.6 years since tour, there was a significant negative association between current dioxin and the percentage of Ranch Hands with an abnormal ECG reading in 1987 (Est. RR=0.66, p=0.025). For Ranch Hands with early tours, the percentages of abnormal ECG readings in 1987 were 15.2, 15.7, and 4.8 percent for low, medium, and high current dioxin.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The percentages of participants who had abnormal ECG readings in 1987 did not differ significantly among the four current dioxin categories in the overall longitudinal analysis (Table 12-28 [e]: p=0.224). However, the percentage of Ranch Hands in the high current dioxin category who had abnormal ECG readings in 1987 was marginally lower than the corresponding percentage of Comparisons in the background category (Est. RR=0.47, 95% C.I.: [0.20,1.14], p=0.094). In contrast, Ranch Hands in the unknown and low current dioxin categories had nonsignificantly higher percentages of abnormal ECG readings than the Comparisons in the background category (p=0.597 and p=0.878, respectively). The relative frequencies of participants with abnormal ECG readings in 1987 were 10.5, 11.9, 11.0, and 5.3 percent for the background, unknown, low, and high current dioxin categories.

DISCUSSION

Circulatory disorders are among the most common diseases encountered by primary care physicians. The sources of the noninvasive data analyzed in the current section occupy a time-honored place in cardiovascular practice, specifically the history, physical examination, chest x ray, and resting ECG. These four are highly reliable indices that alert the clinician to the presence of underlying cardiovascular disease and point to the need for additional, more specific, noninvasive or invasive studies. Though arbitrary, dividing data collection into central and peripheral cardiovascular functions is convenient and forms a reasonable basis for contrasting study participants.

The limitations of the history in cardiovascular diagnosis deserve emphasis. In peripheral vascular disease, for example, signs and symptoms vary depending on the degree of development of collateral circulatory channels. While hemodynamically significant arterial disease of the lower extremities usually is associated with claudication, severe carotid occlusive disease can be present in the absence of symptoms of transient cerebral ischemia. Furthermore, conclusive evidence shows that advanced coronary artery disease can occur in the absence of angina and be present as "silent" myocardial ischemia (24). Cardiovascular history, as related by patients, is often subject to error. The generic term *heart attack*, for example, can be used to describe any type of cardiac event from an isolated episode of unstable angina or arrhythmia to an actual myocardial infarction. These imperfections highlight the importance of the type of medical record verification conducted in the current study.

The physical examination can provide valuable clues to the presence of asymptomatic but significant underlying disease, particularly in the cardiovascular assessment. Because the examinations in this study were conducted by internists rather than cardiologists, steps were taken to simplify data collection and to reduce interobserver differences among the examining physicians. All blood pressure readings, for example, were taken by automated sphygmomanometric instruments. Auscultory endpoints (murmurs and bruits) were recorded as present or absent by anatomic location, thus eliminating speculation as to specific valvular or vessel origin and hemodynamic significance. As markers of occult arterial occlusive disease, vascular bruits, which are relatively easy to detect, were carefully sought over the carotid, abdominal, and femoral vessels.

Pertinent to the longitudinal design of the AFHS, several of the physical findings recorded must be viewed in the context of the aging population under study. A gradual increase in systolic blood pressure occurs with advancing years. Related to the normal progression of arteriosclerosis and, more specifically, to arterial tortuosity, vascular bruits may occur in vessels free of occlusive disease, particularly in the carotid arteries. All bruits were recorded by location without attempting to comment on the hemodynamic significance or specific vessel of origin (i.e., internal versus external carotid). The occurrence of abnormal heart sounds, particularly S_4, also increases with age.

The laboratory data collected in the current section were limited to the resting 12-lead ECG and the standard two-view chest x ray (discussed in Chapter 17, Pulmonary Assessment). In current practice, these techniques are supplemented, but not replaced, by such noninvasive studies as the treadmill exercise test, nuclear isotope studies, and the echocardiogram. These more sophisticated procedures generally serve to confirm diagnoses that can be made based on the more basic techniques. For example, when correlated with the history and physical examination, the chest x ray and ECG enable the clinician to draw highly accurate conclusions regarding the presence and hemodynamic significance of valvular heart disease of any etiology. As defined by the chest x ray, the pulmonary vascularity can provide reliable clues to the presence of global left ventricular dysfunction with pulmonary venous congestion and the presence of pulmonary hypertension.

Analysis of the historical variables examined revealed no evidence for any increased incidence of cardiovascular disease associated with the current or extrapolated initial levels of serum dioxin. In several of the analyses, Ranch Hand participants with higher levels of

serum dioxin appeared to be less at risk than Ranch Hands with lower serum levels and Comparisons. In the maximal cohort, for example, the incidence of reported and verified heart disease in Ranch Hands decreased as the initial serum levels of the Ranch Hands became higher (unadjusted: p=0.007 and 0.006, respectively; adjusted: p=0.052 and p=0.044, respectively). Though not as statistically significant, a similar inverse dose-response relationship was noted in the analysis of current serum dioxin levels. Comparisons appeared to be at greater risk for heart disease than Ranch Hands in the high current dioxin category and the incidence of myocardial infarction was similar in both cohorts.

With rare exception, none of the central cardiac physical examination variables was associated positively with the body burden of dioxin. Ranch Hand participants with the highest levels of extrapolated initial serum dioxin had higher systolic blood pressure by continuous analysis than Ranch Hands with medium and lower levels. Though statistically significant (p=0.049), the differences were slight (133.12, 129.73, and 128.31 mm Hg for high, medium, and low levels of TCDD). According to the more clinically relevant discrete analysis, there was no evidence for a dose-response effect. None of the other indices of central cardiac function (including ECG) showed any increase in risk related to the current or extrapolated initial levels of serum dioxin.

In the analysis of peripheral vascular function, several positive associations were noted in relation to the current and extrapolated initial levels of serum dioxin. Unadjusted for such established risk factors as serum cholesterol and percent body fat, Ranch Hand participants with the highest levels of current serum dioxin were found to have higher mean diastolic blood pressure than Comparisons. Although consistent with a dose-response effect, the means were both within normal limits and the difference was slight (76.71 mm Hg and 74.64 mm Hg, respectively). Finally, although a higher incidence of dorsalis pedis pulse deficits was noted in association with the extrapolated initial serum dioxin (low, 9.4%; medium, 11.6%; high, 15.2%), only those participants less removed from service in Vietnam showed evidence for a dose-response effect in relation to the current serum dioxin level. However, these were isolated findings limited to one of the peripheral arterial pulses examined and the three highly correlated composite pulse indices (correlation>0.98).

SUMMARY

Table 12-29 summarizes the results of the initial dioxin analyses for the variables investigated in 1987 for the cardiovascular examination, Table 12-30 presents the results of the current dioxin and time since tour analyses, and Table 12-31 displays the results of the categorized current dioxin analyses. Table 12-32 presents a summary of the interactions found in the course of the three primary analyses.

Questionnaire Variables

Three variables—essential hypertension, heart disease (excluding essential hypertension), and myocardial infarction—concerning cardiovascular disease were constructed from questionnaire information and augmented by physical examination determinations. These conditions were later verified by medical records review. All reported cases of essential hypertension and myocardial infarction were verified; however, there were fewer verified cases of heart disease than reported cases of heart disease.

TABLE 12-29.

Summary of Initial Dioxin Analyses for Cardiovascular Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted		Adjusted	
Variable	Minimal	Maximal	Minimal	Maximal
Questionnaire				
Reported/Verified Essential Hypertension (D)	NS	NS*	NS	** (NS)
Reported Heart Disease (Excluding Essential Hypertension) (D)	ns	-0.007	** (ns)	ns*
Verified Heart Disease (Excluding Essential Hypertension) (D)	ns	-0.006	** (ns)	-0.044
Reported/Verified Myocardial Infarction (D)	ns	NS	NS	NS
Physical Examination: Central Cardiac Function				
Systolic Blood Pressure (C)	NS	NS	*** (NS)	** (NS)
Systolic Blood Pressure[a] (C)	--	--	** (NS)	** (+0.049)
Systolic Blood Pressure (D)	ns	NS	** (ns)	NS
Heart Sounds (D)	ns	ns	NS	NS
Overall Electrocardiograph (D)	ns	ns	NS	NS
ECG: Right Bundle Branch Block (D)	NS	NS	--	--
ECG: Nonspecific ST- and T-Wave Changes (D)	ns	NS	ns	NS
ECG: Bradycardia (D)	ns	ns*	ns	ns*
ECG: Arrhythmia (D)	NS	NS	** (NS*)	NS
ECG: Other Diagnoses (D)	ns	ns	ns	ns

TABLE 12-29. (Continued)

Summary of Initial Dioxin Analyses for Cardiovascular Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted		Adjusted	
Variable	Minimal	Maximal	Minimal	Maximal
Physical Examination: Peripheral Vascular Function				
Diastolic Blood Pressure (C)	NS	NS	NS	****
Diastolic Blood Pressure (D)	ns	NS	ns	NS
Funduscopic Examination (D)	NS	ns	--	--
Carotid Bruits (D)	ns	ns	ns	ns
Femoral Pulses (D)	ns	NS	** (NS)	** (NS)
Popliteal Pulses (D)	ns	ns	ns	NS
Dorsalis Pedis Pulses (D)	NS	NS*	** (NS)	+0.041
Posterior Tibial Pulses (D)	ns	NS	NS	NS*
Posterior Tibial Pulses[a] (D)	--	--	NS	NS
Leg Pulses (D)	NS	NS*	** (NS)	+0.021
Leg Pulses[a] (D)	--	--	** (NS)	--
Peripheral and All Pulses (D)	NS	NS*	** (NS)	+0.025

[a]Adjusted results from models without cholesterol and/or percent body fat presented for this variable; see Appendix K-2 for a detailed description of these analyses.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.

-: Relative risk less than 1.00 for discrete analysis.

--: Analyses not applicable, or analyses were not performed due to the sparse number of abnormalities.

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

NS*/ns*: Marginally significant ($0.05<p\leq0.10$).

** (NS)/** (ns): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table K-1 or K-3 for a detailed description of this interaction.

** (NS*): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$), marginally significant when interaction is deleted; refer to Appendix Table K-1 for a detailed description of this interaction.

** (0.049): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$), significant ($p=0.049$) when interaction is deleted; refer to Appendix Table K-3 for a detailed description of this interaction.

TABLE 12-29. (Continued)

Summary of Initial Dioxin Analyses for Cardiovascular Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

*** (NS): Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); not significant when interaction is deleted; refer to Appendix Table K-1 for a detailed description of this interaction.

****: Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); refer to Appendix Table K-1 for a detailed description of this interaction.

Note: P-value given if $p \leq 0.05$.
A capital "NS" denotes relative risk 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.

TABLE 12-30.

Summary of Current Dioxin and Time Analyses for Cardiovascular Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Reported/Verified Essential Hypertension (D)	ns	NS	NS	ns	NS	NS
Reported Heart Disease (Excluding Essential Hypertension) (D)	NS	ns	ns	ns	ns*	-0.015
Verified Heart Disease (Excluding Essential Hypertension) (D)	NS	ns	ns	ns	ns*	-0.013
Reported/Verified Myocardial Infarction (D)	ns	ns	ns	ns	NS	ns
Physical Examination: Central Cardiac Function						
Systolic Blood Pressure (C)	NS	NS	NS	NS	NS	NS
Systolic Blood Pressure (D)	ns	NS	ns	ns	NS	NS
Heart Sounds (D)	NS	ns	ns	NS	ns	NS
Overall Electrocardiograph (D)	ns	NS	ns	ns	NS	ns
ECG: Right Bundle Branch Block (D)	- -	- -	NS	- -	- -	NS
ECG: Nonspecific ST- and T-Wave Changes (D)	ns	ns	ns	ns	NS	ns
ECG: Bradycardia (D)	ns	NS	ns	ns*	NS	ns*
ECG: Arrhythmia (D)	ns	NS	NS	-0.032	NS*	ns
ECG: Other Diagnoses (D)	ns	NS	-0.048	-0.040	NS	-0.011
Physical Examination: Peripheral Vascular Function						
Diastolic Blood Pressure (C)	ns	NS	NS	NS	NS	NS

TABLE 12-30. (Continued)

Summary of Current Dioxin and Time Analyses for Cardiovascular Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Physical Examination: Peripheral Vascular Function (continued)						
Diastolic Blood Pressure (D)	NS	ns	ns	NS	ns	NS
Funduscopic Examination (D)	- -	NS	- -	- -	NS	- -
Carotid Bruits (D)	- -	- -	ns	- -	- -	ns
Femoral Pulses (D)	ns	ns	ns	ns	NS	ns
Popliteal Pulses (D)	NS	ns	ns	ns	ns	ns
Dorsalis Pedis Pulses (D)	ns	NS	ns	ns	NS	NS
Posterior Tibial Pulses (D)	NS	ns	ns	ns	NS	NS
Leg Pulses (D)	ns	NS	ns	ns	NS	NS
Peripheral and All Pulses (D)	ns	NS	ns	ns	NS	NS

C: Continuous analysis.
D: Discrete analysis.
-: C*T: Relative risk for ≤18.6 category greater than relative risk for >18.6 category.
≤18.6 and >18.6: Relative risk less than 1.00 for discrete analysis.
--: Analyses were not performed due to the sparse number of abnormalities.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour more than 18.6 years.
A capital "NS" denotes relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category, relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk/slope for ≤18.6 category greater than relative risk/slope for >18.6 category or relative risk less than 1.00 for discrete analysis.

TABLE 12-30. (Continued)

Summary of Current Dioxin and Time Analyses for Cardiovascular Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Reported/Verified Essential Hypertension (D)	ns	NS	ns	ns	NS	NS
Reported/Verified Essential Hypertension[a] (D)	ns	NS	NS	ns	+0.023	NS
Reported Heart Disease (Excluding Essential Hypertension) (D)	ns	ns	ns	ns	ns	ns*
Verified Heart Disease (Excluding Essential Hypertension) (D)	ns	ns	ns	ns	ns	ns*
Reported/Verified Myocardial Infarction (D)	ns	NS	NS	ns	NS*	NS
Physical Examination: Central Cardiac Function						
Systolic Blood Pressure (C)	** (ns)	** (ns)	** (ns)	** (NS)	** (NS)	** (NS)
Systolic Blood Pressure (D)	****	****	****	** (ns)	** (NS)	** (ns)
Heart Sounds (D)	****	****	****	****	****	****
Overall Electrocardiograph (D)	ns	NS*	ns	ns	NS	ns
ECG: Right Bundle Branch Block (D)	--	--	--	--	--	--
ECG: Nonspecific ST- and T-Wave Changes (D)	ns	NS	ns	** (ns)	** (NS)	** (NS)
ECG: Bradycardia (D)	ns	NS	ns	ns*	NS	ns*
ECG: Arrhythmia (D)	ns	+0.017	NS	** (-0.034)	** (+0.018)	** (ns)
ECG: Other Diagnoses (D)	ns	NS	ns	-0.026	NS	-0.046

TABLE 12-30. (Continued)

Summary of Current Dioxin and Time Analyses for Cardiovascular Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Physical Examination: Peripheral Vascular Function						
Diastolic Blood Pressure (C)	ns	NS	ns	NS	ns	NS
Diastolic Blood Pressure (D)	NS	ns	ns	NS	ns	NS
Funduscopic Examination (D)	--	--	--	--	--	--
Carotid Bruits (D)	--	--	--	--	--	--
Femoral Pulses (D)	ns	NS	ns	****	****	****
Popliteal Pulses (D)	** (NS)	** (ns)	** (ns)	** (ns)	** (ns)	** (ns)
Dorsalis Pedis Pulses (D)	ns	NS*	NS	ns	+0.048	NS
Posterior Tibial Pulses (D)	ns	NS	ns	ns	NS*	NS
Posterior Tibial Pulses[a] (D)	ns	ns	ns	ns	NS	NS
Leg Pulses (D)	** (ns)	** (NS)	** (ns)	ns	NS*	NS
Peripheral and All Pulses (D)	** (ns)	** (NS)	** (ns)	ns	NS*	NS

[a]Adjusted results from models without cholesterol and/or percent body fat presented for this variable; see Appendix K-2 for a detailed description of these analyses.

C: Continuous analysis.

D: Discrete analysis.

+: ≤18.6 and >18.6: Relative risk 1.00 or greater for discrete analysis.

-: C*T: Relative risk for ≤18.6 category greater than relative risk for >18.6 category.
≤18.6 and >18.6: Relative risk less than 1.00 for discrete analysis.

--: Analyses were not performed due to the sparse number of abnormalities.

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

NS*/ns*: Marginally significant ($0.05<p\leq0.10$).

** (NS)/** (ns): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table K-1 for a detailed description of this interaction.

** (...): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table K-1 for a detailed description of this interaction.

****: Log_2 (current dioxin)-by-time-by-covariate interaction ($p\leq0.01$); refer to Appendix Table K-1 for a detailed description of this interaction.

TABLE 12-30. (Continued)

Summary of Current Dioxin and Time Analyses for Cardiovascular Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

Note: P-value given if $p \leq 0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour more than 18.6 years.
A capital "NS" denotes relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category, relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk/slope for ≤18.6 category greater than relative risk/slope for >18.6 category, relative risk less than 1.00 for discrete analysis, or slope negative for continuous analysis.

TABLE 12-31.

Summary of Categorized Current Dioxin Analyses for Cardiovascular Variables (Ranch Hands and Comparisons)

Variable	All	Unadjusted: Unknown versus Background	Unadjusted: Low versus Background	Unadjusted: High versus Background
Questionnaire				
Reported/Verified Essential Hypertension (D)	0.043	ns	NS	NS
Reported Heart Disease (Excluding Essential Hypertension) (D)	0.003	+0.047	ns	-0.010
Verified Heart Disease (Excluding Essential Hypertension) (D)	0.002	NS*	ns	-0.007
Reported/Verified Myocardial Infarction (D)	NS*	ns	NS	ns
Physical Examination: Central Cardiac Function				
Systolic Blood Pressure (C)	NS	ns	NS	NS
Systolic Blood Pressure (D)	NS	ns	ns	NS
Heart Sounds (D)	NS	ns	ns	ns
Overall Electrocardiograph (D)	NS	ns	ns	ns
ECG: Right Bundle Branch Block (D)	NS	ns	NS	ns
ECG: Nonspecific ST- and T-Wave Changes (D)	NS	ns	NS	NS
ECG: Bradycardia (D)	NS	NS	ns	ns
ECG: Arrhythmia (D)	NS	NS	ns	NS
ECG: Other Diagnoses (D)	0.024	NS	NS	-0.007

TABLE 12-31. (Continued)

Summary of Categorized Current Dioxin Analyses for Cardiovascular Variables (Ranch Hands and Comparisons)

Variable	All	Unadjusted: Unknown versus Background	Unadjusted: Low versus Background	Unadjusted: High versus Background
Physical Examination: Peripheral Vascular Function				
Diastolic Blood Pressure (C)	0.017	ns	+0.028	NS*
Diastolic Blood Pressure (D)	NS	ns	NS	NS
Funduscopic Examination (D)	NS	NS	ns	NS
Carotid Bruits (D)	NS	NS	NS	ns
Femoral Pulses (D)	NS	NS	NS	NS
Popliteal Pulses (D)	NS	NS	NS	ns
Dorsalis Pedis Pulses (D)	NS	NS	NS*	NS
Posterior Tibial Pulses (D)	<0.001	ns	+0.003	ns
Leg Pulses (D)	NS*	NS	+0.010	NS
Peripheral Pulses (D)	NS	NS	+0.016	NS
All Pulses (D)	NS	NS	+0.019	NS

C: Continuous analysis.
D: Discrete analysis.
+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.
-: Relative risk less than 1.00 for discrete analysis.
NS/ns: Not significant ($p>0.10$).
NS*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference 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; a capital "NS" in the first column does not imply directionality.

TABLE 12-31. (Continued)

Summary of Categorized Current Dioxin Analyses for Cardiovascular Variables (Ranch Hands and Comparisons)

Variable	All	Adjusted: Unknown versus Background	Adjusted: Low versus Background	Adjusted: High versus Background
Questionnaire				
Reported/Verified Essential Hypertension (D)	** (NS)	** (ns)	** (NS)	** (NS*)
Reported/Verified Essential Hypertension[a] (D)	** (0.002)	** (ns*)	** (NS)	** (+0.006)
Reported Heart Disease (Excluding Essential Hypertension) (D)	0.024	NS*	ns	ns*
Verified Heart Disease (Excluding Essential Hypertension) (D)	0.021	NS*	ns	-0.049
Reported/Verified Myocardial Infarction (D)	****	****	****	****
Physical Examination: Central Cardiac Function				
Systolic Blood Pressure (C)	*** (NS)	*** (ns)	*** (NS)	*** (NS)
Systolic Blood Pressure[a] (C)	** (0.012)	** (ns*)	** (NS)	** (+0.019)
Systolic Blood Pressure (D)	****	****	****	****
Heart Sounds (D)	NS	ns	ns	NS
Overall Electrocardiograph (D)	NS	ns*	NS	NS
ECG: Right Bundle Branch Block (D)	NS	ns	NS	- -
ECG: Nonspecific ST- and T-Wave Changes (D)	NS	ns	NS	NS
ECG: Bradycardia (D)	** (NS)	** (NS)	** (ns)	** (ns)
ECG: Bradycardia[a] (D)	** (NS)	** (NS)	** (ns)	** (ns*)
ECG: Arrhythmia (D)	NS	NS	ns	NS*

TABLE 12-31. (Continued)

Summary of Categorized Current Dioxin Analyses for Cardiovascular Variables (Ranch Hands and Comparisons)

Variable	All	Adjusted: Unknown versus Background	Adjusted: Low versus Background	Adjusted: High versus Background
Physical Examination: Central Cardiac Function (continued)				
ECG: Other Diagnoses (D)	NS	ns	NS	-0.036
Physical Examination: Peripheral Vascular Function				
Diastolic Blood Pressure (C)	*** (NS*)	*** (ns)	*** (+0.032)	*** (NS*)
Diastolic Blood Pressure[a] (C)	** (0.002)	** (ns)	** (+0.020)	** (+0.017)
Diastolic Blood Pressure (D)	NS	ns	NS	NS
Funduscopic Examination (D)	** (NS)	** (NS)	** (ns)	** (NS)
Carotid Bruits (D)	NS	NS	NS	--
Femoral Pulses (D)	** (NS)	** (NS)	** (NS*)	** (+0.049)
Popliteal Pulses (D)	NS	ns	NS	NS
Dorsalis Pedis Pulses (D)	NS	NS	NS*	NS*
Dorsalis Pedis Pulses[a] (D)	NS*	NS	NS*	+0.029
Posterior Tibial Pulses (D)	<0.001	ns	+<0.001	NS
Leg Pulses (D)	0.020	NS	+0.005	+0.047
Peripheral Pulses (D)	0.017	NS	+0.007	+0.033
All Pulses (D)	0.021	NS	+0.008	+0.035

TABLE 12-31. (Continued)

Summary of Categorized Current Dioxin Analyses for Cardiovascular Variables (Ranch Hands and Comparisons)

[a]Adjusted results from models without cholesterol and/or percent body fat presented for this variable; see Appendix K-2 for a detailed description of these analyses.
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.
-: Relative risk less than 1.00 for discrete analysis.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
** (NS)/** (ns): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table K-1 or K-3 for a detailed description of this interaction.
*** (NS)/*** (ns): Categorized current dioxin-by-covariate interaction ($p\leq0.01$); not significant when interaction is deleted; refer to Appendix Table K-1 for a detailed description of this interaction.
** (NS*)/** (ns*): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); marginally significant when interaction is deleted; refer to Appendix Table K-1 or K-3 for a detailed description of this interaction.
*** (NS*): Categorized current dioxin-by-covariate interaction ($p\leq0.01$); marginally significant when interaction is deleted; refer to Appendix Table K-1 for a detailed description of this interaction.
** (...): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table K-1 or K-3 for a detailed description of this interaction.
*** (...): Categorized current dioxin-by-covariate interaction ($p\leq0.01$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table K-1 for a detailed description of this interaction.
****: Categorized current dioxin-by-covariate interaction ($p\leq0.01$); refer to Appendix Table K-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference 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; a capital "NS" in the first column does not imply directionality.

TABLE 12-32.

Summary of Dioxin-by-Covariate Interactions from Adjusted Analyses of Cardiovascular Variables

Variable	Assumption	Covariate
Model 1: Ranch Hands - Log_2 (Initial Dioxin)		
Reported/Verified Essential Hypertension	Maximal	DIFCORT
Reported Heart Disease (Excluding Essential Hypertension)	Minimal	RACE
Verified Heart Disease (Excluding Essential Hypertension)	Minimal	RACE
Systolic Blood Pressure (Continuous)	Minimal	AGE,PACKYR
Systolic Blood Pressure (Continuous)	Maximal	PACKYR
Systolic Blood Pressure (Discrete)	Minimal	PERS
ECG: Arrhythmia	Minimal	PERS
Diastolic Blood Pressure (Continuous)	Maximal	PERS
Femoral Pulses	Minimal	PERS
Femoral Pulses	Maximal	PERS
Dorsalis Pedis Pulses	Minimal	DIFCORT
Leg Pulses	Minimal	AGE
Peripheral and All Pulses	Minimal	AGE
Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time		
Systolic Blood Pressure (Continuous)	Minimal	HRTDIS
Systolic Blood Pressure (Continuous)	Maximal	AGE
Systolic Blood Pressure (Discrete)	Minimal	PERS
Systolic Blood Pressure (Discrete)	Maximal	PERS
Heart Sounds	Minimal	HRTDIS,PACKYR
Heart Sounds	Maximal	HRTDIS,PACKYR
ECG: Nonspecific ST- and T-Wave Changes	Maximal	AGE
ECG: Arrhythmia	Maximal	DIFCORT
Femoral Pulses	Maximal	%BFAT,DIFCORT
Popliteal Pulses	Minimal	HRTDIS
Popliteal Pulses	Maximal	PACKYR
Leg Pulses	Minimal	PACKYR
Peripheral and All Pulses	Minimal	PACKYR

TABLE 12-32. (Continued)

Summary of Dioxin-by-Covariate Interactions from Adjusted Analyses of Cardiovascular Variables

Variable	Assumption	Covariate
Model 3: Ranch Hands and Comparisons by Current Dioxin Category		
Reported/Verified Essential Hypertension	- -	AGE
Reported/Verified Myocardial Infarction	- -	DIFCORT
Systolic Blood Pressure (Continuous)	- -	AGE
Systolic Blood Pressure (Discrete)	- -	AGE,DIFCORT
ECG: Bradycardia	- -	RACE
Diastolic Blood Pressure (Continuous)	- -	PERS,HRTDIS
Funduscopic Examination	- -	DIFCORT
Femoral Pulses	- -	PERS

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the unadjusted and adjusted analyses of the questionnaire variables did not display any significant associations with initial dioxin. The unadjusted maximal analyses detected significant negative associations with initial dioxin for reported and verified heart disease (Table 12-29: p=0.007 and p=0.006, respectively) and a marginally significant positive association for reported/verified essential hypertension. Under the maximal assumption, the adjusted analyses detected a marginally significant negative association between initial dioxin and reported heart disease and a significant negative association for verified heart disease (Table 12-29: p=0.044). In addition, the adjusted maximal analysis of reported/verified essential hypertension detected a significant initial dioxin-by-differential cortisol response interaction. Stratified analyses of this interaction revealed no significant results. There were also initial dioxin-by-race interactions found in the minimal analyses of both reported and verified heart disease. These interactions exhibited significant negative associations between initial dioxin and heart disease for Blacks and nonsignificant negative associations between initial dioxin and heart disease for non-Blacks. After deletion of all three of these interactions from the adjusted models, the analyses were nonsignificant.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The unadjusted minimal analyses of the questionnaire variables did not reveal any significant results; however, the associations of current dioxin with heart disease and myocardial infarction were negative within both time since tour strata. Under the maximal assumption, the interactions between current dioxin and time since tour were also nonsignificant. The maximal unadjusted analyses of both reported and verified heart disease detected marginally significant negative associations with current dioxin for Ranch Hands with later tours and significant negative associations with current dioxin for Ranch Hands with early tours (Table 12-30: p=0.015 and p=0.013, respectively).

Similar to the unadjusted results, the minimal analyses of the questionnaire variables remained nonsignificant after adjustment for covariate information. The inclusion of covariates in the maximal model caused the negative associations between current dioxin and both reported and verified heart disease to become nonsignificant for Ranch Hands with 18.6 years or less since tour and marginally significant for Ranch Hands with more than 18.6 years since tour. Also, for Ranch Hands with 18.6 years or less since tour, the maximal adjusted analysis of reported/verified myocardial infarction detected a marginally significant positive association with current dioxin.

In addition, after removing percent body fat from the maximal analysis of reported/verified essential hypertension, the positive association with current dioxin became significant for Ranch Hands with later tours (Table 12-30: p=0.023).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the questionnaire variables detected significant differences among the four current dioxin categories for reported/verified essential hypertension (Table 12-31: p=0.043) and reported and verified heart disease excluding essential hypertension (p=0.003 and p=0.002). The Ranch Hands in the unknown category had a significantly higher reported incidence of heart disease (p=0.047) and a marginally higher verified incidence of

heart disease than the Comparisons in the background category. Also, the Ranch Hands in the high current dioxin category had significantly lower reported and verified incidence of heart disease than the Comparisons in the background category (p=0.010 and p=0.007, respectively). In addition, in the unadjusted analysis of reported/verified myocardial infarction, the overall contrast of the four current dioxin categories was marginally significant.

After adjusting for covariate information, the overall contrast of the four current dioxin categories remained significant for reported and verified heart disease (Table 12-31: p=0.024 and p=0.021, respectively). However, the contrast of the Ranch Hands in the unknown category versus the Comparisons in the background category became marginally significant. Similarly, in the adjusted analyses, the Ranch Hands in the high category had only a marginally lower risk of reported heart disease and a significantly lower risk of verified heart disease (p=0.049) than the Comparisons in the background category.

The adjusted analysis of reported/verified essential hypertension revealed a significant interaction between categorized current dioxin and age, and similarly, the analysis of reported/verified myocardial infarction detected a significant interaction between categorized current dioxin and differential cortisol response. Stratified results did not indicate a dioxin effect for either variable. After deletion of the interaction, the analysis of reported/verified essential hypertension no longer found a significant difference among the four current dioxin categories. The contrast of the Ranch Hands in the high category versus the Comparisons in the background category became marginally significant. However, after excluding percent body fat and the categorized current dioxin-by-age interaction from the model, the simultaneous contrast of the incidence of essential hypertension of the four current dioxin categories was significant (Table 12-31: p=0.002). Also, the Ranch Hands in the high current dioxin category had a significantly higher risk of essential hypertension than the Comparisons in the background category (p=0.005).

Physical Examination: Central Cardiac Function Variables

Variables analyzed in the evaluation of the central cardiac function included systolic blood pressure, heart sounds, and seven conditions associated with the ECG (overall ECG reading, RBBB, LBBB, nonspecific ST- and T-wave changes, bradycardia, arrhythmia, and other diagnoses). However, there were only three Comparisons and one Ranch Hand diagnosed with LBBB; thus, relative risks, confidence intervals, and p-values were not presented. There were no Ranch Hands and only one Comparison with tachycardia; consequently, no analyses were performed on this cardiovascular endpoint.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted initial dioxin analyses of the central cardiac function variables, only one variable displayed a marginally significant association with initial dioxin under either assumption. The unadjusted analysis of bradycardia detected a marginally significant negative association with initial dioxin under the maximal assumption.

After adjusting for covariate information, the maximal analysis of bradycardia remained marginally significant. Also, the adjusted analyses found significant initial dioxin-by-covariate interactions for systolic blood pressure (both continuous and discrete) and arrhythmia (Table 12-32). The stratified analysis of the interactions for systolic blood

pressure in its continuous form did not exhibit a significant positive association with initial dioxin. The results of the minimal and maximal analyses of systolic blood pressure in its continuous form remained nonsignificant after deletion of the interactions from the model. However, after further deletion of cholesterol and percent body fat, the maximal analysis detected a significant positive association between systolic blood pressure and initial dioxin (Table 12-29: p=0.049).

For discretized systolic blood pressure under the minimal assumption, the stratified analyses of the initial dioxin-by-personality type interaction found a significant decreasing association between the prevalence of abnormally high systolic blood pressure and initial dioxin for Ranch Hands with type A personalities. In contrast, for type B Ranch Hands, there was a nonsignificant positive association with initial dioxin. After the deletion of this interaction, the results were nonsignificant.

An interaction between initial dioxin and personality type was significant for the minimal analysis of arrhythmia. There was a significant positive association between initial dioxin and arrhythmia for type A Ranch Hands and a nonsignificant positive association for type B Ranch Hands. After deletion of this interaction, the minimal adjusted analysis of arrhythmia detected a marginally significant positive association with initial dioxin.

The longitudinal analyses of the minimal and maximal cohorts detected significant negative associations between the percentage of Ranch Hands having an abnormal ECG reading at the 1987 examination and initial dioxin (p=0.014 and p=0.041, respectively).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The association between current dioxin and the central cardiac function variables did not differ significantly between time since tour strata for most unadjusted analyses. Under the minimal assumption, the current dioxin-by-time interaction was not significant for any analyses. However, in the unadjusted analysis of Ranch Hands with early tours, the variable of other ECG diagnoses was negatively associated with current dioxin (Table 12-30: p=0.048). Under the maximal assumption, the current dioxin-by-time since tour interaction was marginally significant in the unadjusted analysis of bradycardia, which also displayed a marginally significant negative association with current dioxin for Ranch Hands with more than 18.6 years since their tour. Also, the unadjusted maximal analyses of arrhythmia and other ECG diagnoses detected significant interactions between current dioxin and time (p=0.032 and p=0.040, respectively). These analyses revealed a marginally significant positive association between current dioxin and arrhythmia for Ranch Hands with later tours and a significant negative association between the overall ECG findings and current dioxin for Ranch Hands with early tours (p=0.011).

The adjusted analysis of the minimal cohort was similar to the corresponding unadjusted analysis. There were no significant current dioxin-by-time since tour interactions for the minimal cohort, but for Ranch Hands with 18.6 years or less since their tour, there was a marginally significant positive association between current dioxin and the overall ECG diagnoses and a significant positive association between current dioxin and arrhythmia (Table 12-30: p=0.017).

For the adjusted analyses under the maximal assumption, the current dioxin-by-time since tour interaction was marginally significant for bradycardia and significant for other ECG diagnoses (Table 12-30: p=0.026). The associations with current dioxin for Ranch Hands with early tours exhibited a similar significance for these two variables (bradycardia: marginally significant negative association; other ECG diagnoses: significant negative association, p=0.046). Also, after deletion of a current dioxin-by-time-by-differential cortisol-response interaction, the maximal adjusted analysis displayed a significant difference in the associations between current dioxin and arrhythmia (p=0.034). There was a positive association between arrhythmia and current dioxin (p=0.018) for Ranch Hands with late tours.

For four of the central cardiac function variables, there were significant interactions among current dioxin, time since tour, and one or more covariates (Table 12-32). The covariates involved in these interactions were age, lifetime cigarette smoking history, personality type, differential cortisol response, and family history of heart disease. All results, except those mentioned above for arrhythmia, were nonsignificant after the deletion of the interactions from the adjusted models.

The longitudinal analysis of the 1987 ECG conditioned on participants with normal ECG readings in 1982 did not detect significant current dioxin-by-time interactions for either the minimal or the maximal cohort. However, there were significant negative associations between current dioxin and the overall ECG reading for Ranch Hands with more than 18.6 years since tour (p=0.013 and p=0.025, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted and adjusted analyses of the central cardiac function variables and categorized current dioxin generally were not significant. In the unadjusted analysis, other ECG diagnoses was the only variable with a significant overall contrast of the four current dioxin categories (Table 12-31: p=0.024). Also, the Ranch Hands in the high current dioxin category had a significantly lower risk of other abnormal ECG diagnoses than the Comparisons in the background category (p=0.007). All other unadjusted results were nonsignificant.

In the adjusted analyses of the central cardiac function variables, the overall contrasts of the four current dioxin categories were not significant except for systolic blood pressure in its continuous form after the deletion of a categorized current dioxin-by-age interaction, cholesterol, and percent body fat (Table 12-31: p=0.012). Also, after these deletions, the Ranch Hands in the unknown current dioxin category had a marginally lower mean systolic blood pressure than the Comparisons in the background category and the Ranch Hands in the high category had a significantly higher mean systolic blood pressure than the Comparisons in the background category (p=0.019).

In the adjusted analyses, the Ranch Hands in the unknown current dioxin category had a marginally lower risk of abnormal overall ECG diagnoses than the Comparisons in the background category. Also, the Ranch Hands in the high current dioxin category had a marginally lower risk of bradycardia (after the deletion of a categorized current dioxin-by-race interaction and percent body fat) and a significantly lower risk of other abnormal ECG

diagnoses than the Comparisons in the background category (Table 12-31: p=0.036). In contrast, the Ranch Hands in the high current dioxin category had a marginally higher risk of arrhythmia than the Comparisons in the background category.

The adjusted analyses revealed significant categorized current dioxin-by-covariate interactions for systolic blood pressure (continuous and discrete) and bradycardia (Table 12-32). Stratified analyses of these interactions did not display any strong dioxin effects for these variables. After deletion of these interactions, the adjusted results generally remained nonsignificant.

In the longitudinal analysis, the percentages of participants who had abnormal ECG readings in 1987 did not differ significantly among the four current dioxin categories. However, the percentage of Comparisons in the background category who had abnormal ECG readings in 1987 was marginally higher than the corresponding percentage of Ranch Hands in the high category (p=0.094).

Physical Examination: Peripheral Vascular Function Variables

The peripheral vascular function was assessed during the cardiovascular examination by the diastolic blood pressure; funduscopic examination of small vessels of the retina; the presence or absence of carotid bruits; and manual palpation of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. In addition, three pulse indices were constructed from the above pulse measurements: leg pulses (femoral, popliteal, dorsalis pedis, and posterior tibial pulses), peripheral pulses (radial and leg pulses), and all pulses (peripheral and carotid pulses). Each of these indices was considered normal if all components were normal and abnormal if one or more pulses were abnormal. There were only two Ranch Hands and four Comparisons with absent radial pulses; thus, relative risks, confidence intervals, and p-values were not presented for this endpoint.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analyses of the peripheral vascular function variables, there were no significant results under the minimal assumption. However, the maximal unadjusted analyses detected marginally significant positive association with current dioxin for dorsalis pedis, leg, peripheral, and all pulses. These marginal associations became significant after adjustment for covariate information (Table 12-29: p=0.041, p=0.021, and p=0.025, respectively). Similarly, under the maximal assumption, the adjusted analysis displayed a marginally significant positive association between initial dioxin and posterior tibial pulses, which became nonsignificant after the deletion of percent body fat from the model.

The adjusted maximal analysis displayed a significant interaction between initial dioxin and personality type for diastolic blood pressure in its continuous form. Stratified analyses of this interaction revealed a marginally significant negative association with initial dioxin for type A Ranch Hands and a significant positive association for type B Ranch Hands (Table 12-29: p=0.015). The adjusted analyses (minimal and maximal) of femoral pulses also displayed significant interactions between initial dioxin and personality type; however, these interactions may have been affected by the sparse number of Ranch Hands with absent femoral pulses. The interactions between initial dioxin and age in the minimal adjusted analyses of leg, peripheral, and all pulses displayed nonsignificant negative associations with

initial dioxin for younger Ranch Hands, but a significant positive association for older Ranch Hands. There was also an interaction between initial dioxin and differential cortisol response for the minimal analysis of dorsalis pedis pulses, which did not show any significant dioxin effects.

After deletion of these initial dioxin-by-covariate interactions from the adjusted models, the results were nonsignificant.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the minimal and the maximal unadjusted analyses of the peripheral vascular function variables, the associations with current dioxin did not differ significantly between the time since tour strata. In general, the relative risks were lower for Ranch Hands with earlier tours than for Ranch Hands with later tours.

In the adjusted analyses, the interactions between current dioxin and time since tour were nonsignificant for both the minimal and the maximal cohorts. However, under the minimal assumption, the adjusted analysis detected a marginally significant positive association between current dioxin and dorsalis pedis pulses for Ranch Hands with 18.6 years or less since tour, which became significant under the maximal assumption (Table 12-30: $p=0.048$). The maximal adjusted analysis of Ranch Hands with 18.6 years or less since tour also detected marginally significant positive associations with current dioxin for abnormal posterior tibial pulses and the leg, peripheral, and all pulses indices. However, after deletion of percent body fat from the adjusted maximal model, the association between current dioxin and abnormal posterior tibial pulses was no longer marginally significant.

The adjusted maximal analysis of femoral pulses revealed significant interactions among current dioxin, time since tour, percent body fat, and differential cortisol response, which were in part caused by the small number of Ranch Hands with abnormal femoral pulses. The analyses of popliteal pulses and the three pulse indices (leg, peripheral, all) detected significant interactions with lifetime cigarette smoking history. Stratified analyses of these interactions displayed a positive association between current dioxin and the dependent variable for heavy smokers with later tours and a negative association for heavy smokers with earlier tours. After deletion of these interactions, the analyses were generally nonsignificant.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analyses of categorized current dioxin and the peripheral vascular function variables generally were nonsignificant. The only variables with significant overall contrasts of the four current dioxin categories were diastolic blood pressure in its continuous form (Table 12-31: $p=0.017$), posterior tibial pulses ($p<0.001$) and the leg pulses index (marginal significance). The contrasts of the Ranch Hands in the unknown current dioxin category and in the high category (except for diastolic blood pressure in its continuous form) versus the Comparisons in the background category were all nonsignificant but generally in a positive direction. However, Ranch Hands in the low current dioxin category had a significantly higher mean diastolic blood pressure ($p=0.028$) and higher risks of abnormal dorsalis pedis pulses (marginal significance), posterior tibial pulses ($p=0.003$), leg pulses ($p=0.010$), peripheral pulses ($p=0.016$), and all pulses ($p=0.019$) than the Comparisons in the

background category. Ranch Hands in the high category also had a marginally higher mean diastolic blood pressure than the Comparisons in the background category.

The adjusted analyses of categorized current dioxin and the peripheral vascular function variables detected a larger number of differences among the four current dioxin categories than the unadjusted analyses (Table 12-31). These analyses revealed significant overall differences among the four current dioxin categories for posterior tibial pulses ($p<0.001$), leg pulses ($p=0.020$), peripheral pulses ($p=0.017$), and all pulses ($p=0.021$). Also, after deletion of categorized current dioxin, personality type, and family history of heart disease interactions from the analysis of diastolic blood pressure in its continuous form, the overall contrast of the four current dioxin categories was marginally significant. In this same analysis, the further exclusion of cholesterol and percent body fat caused the overall contrast to become significant ($p=0.002$). Similarly, the deletion of cholesterol from the adjusted analysis of dorsalis pedis pulses caused the overall contrast of the four current dioxin categories to become marginally significant.

Consistent with the unadjusted results, the adjusted analyses did not detect any significant differences in the peripheral vascular function variables between the Ranch Hands in the unknown current dioxin category and the Comparisons in the background category (Table 12-31). However, the Ranch Hands in the low current dioxin category had a significantly higher mean diastolic blood pressure ($p=0.032$ after deletion of interactions) and significantly higher risks of abnormal posterior tibial pulses ($p<0.001$), leg pulses ($p=0.005$), peripheral pulses ($p=0.007$), and all pulses ($p=0.008$) than the Comparisons in the background category. These Ranch Hands also had marginally higher risks of abnormal femoral pulses (after deletion of a categorized current dioxin-by-personality type interaction) and dorsalis pedis pulses.

The Ranch Hands in the high current dioxin category had significantly higher risks of abnormal femoral pulses (Table 12-31: $p=0.049$, after deletion of categorized current dioxin-by-personality type interaction), leg pulses ($p=0.047$), peripheral pulses ($p=0.033$), and all pulses ($p=0.035$). After deletion of interactions, the adjusted analysis also revealed a marginally higher mean diastolic blood pressure for Ranch Hands in the high current dioxin category than for Comparisons in the background category; this contrast became significant after the deletion of cholesterol and percent body fat from the model ($p=0.017$). Similarly, the Ranch Hands in the high current dioxin category had a marginally higher risk of abnormal dorsalis pedis pulses than the Comparisons; this contrast also became significant after the deletion of cholesterol from the adjusted model ($p=0.029$).

The analyses of the peripheral vascular function variables discovered interactions between categorized current dioxin and personality type, differential cortisol response, and family history of heart disease (Table 12-32). The stratified analyses of these interactions failed to detect any significant dioxin effects or covariate trends. However, these interactions may have been affected by the sparse number of abnormalities of several of the peripheral vascular function variables. Results after the deletion of these interactions were nonsignificant unless otherwise discussed above.

CONCLUSION

The cardiovascular evaluation found a marginal association between initial dioxin and a decrease in the incidence of reported heart disease and a significant negative association with verified heart disease in the maximal cohort. Analyses displayed similar marginally significant negative associations only for Ranch Hands with early tours of duty in Vietnam under the maximal assumption. In addition, the analyses of categorized current dioxin also indicated a decreased incidence of verified heart disease for Ranch Hands with the highest current dioxin levels relative to the Comparisons with background levels. These Ranch Hands also displayed an increased incidence of essential hypertension (after removing percent body fat and cholesterol from the model).

In general, the analyses of the central cardiac function variables were not positively associated with dioxin. By continuous analysis, Ranch Hands under the maximal assumption exhibited a significant positive association between initial serum levels and systolic blood pressure when percent body fat was not considered. This finding was not significant after adjustment for percent body fat, and in no models was initial dioxin associated significantly with abnormally high levels of systolic blood pressure.

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 percent 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 the Comparisons. Due to the high correlation of the leg pulse variables and the composite pulse indices, it is not surprising that the leg, peripheral, and all pulse indices displayed a significant positive association with dioxin. These pulses will be further evaluated at the 1992 physical examination. These observations could represent a subclinical effect and emphasize the importance of continued followup and evaluation in subsequent examination phases of the study.

Longitudinal analyses of the overall ECG displayed significant negative associations with dioxin.

In general, the development of nondiabetes-related cardiovascular disease does not appear to be associated positively with dioxin; however, there were significant associations between dioxin and peripheral pulse deficits and systolic blood pressure. The cardiovascular assessment was primarily based on nondiabetics only. Additional analyses based on diabetics only were done for myocardial infarction and leg pulses; no significant results were found in these analyses.

CHAPTER 12

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