Air Force Health Study

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

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SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS

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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 (≥100°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) RACE (p=0.138)
Unknown	320	Unknown vs. Background	1.30 (0.99,1.71)	0.055	
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						0.862[b]
(n=446)	≤18.6	5.1 (59)	5.3 (113)	2.2 (46)	0.90 (0.48,1.70)	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						0.332[b]
(n=647)	≤18.6	1.0 (103)	4.8 (167)	2.9 (68)	1.25 (0.80,1.96)	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			0.705[b]	AGE (p<0.001)
(n=440)	≤18.6	1.23 (0.62,2.44)	0.554[c]	DRKYR (p=0.038)
	>18.6	1.05 (0.64,1.72)	0.859[c]	
h) Maximal			0.159[b]	AGE (p<0.001)
(n=634)	≤18.6	1.63 (0.98,2.69)	0.058[c]	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						0.961[b]
(n=446)	≤18.6	128.36	125.81	128.43	0.017 (1.078)	0.987[c]
(R^2=0.002)		(59)	(113)	(46)		
	>18.6	127.80	129.04	128.55	0.087 (0.914)	0.924[c]
		(49)	(115)	(64)		
f) Maximal						0.781[b]
(n=647)	≤18.6	126.29	126.75	126.76	0.263 (0.731)	0.719[c]
(R^2=0.003)		(103)	(167)	(68)		
	>18.6	125.56	128.17	129.93	0.540 (0.679)	0.427[c]
		(68)	(154)	(87)		

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						0.935**[b]	CURR*TIME*HRTDIS
(n=431)	≤18.6	130.40**	129.11**	134.68**	-0.318 (1.106)**	0.774**[c]	(p=0.048)
(R^2=0.084)		(56)	(109)	(42)			RACE (p=0.078)
	>18.6	131.94**	132.77**	131.13**	-0.433 (0.902)**	0.632**[c]	CHOL (p=0.009)
		(48)	(113)	(63)			%BFAT (p<0.001)
							PERS (p=0.105)
h) Maximal						0.727**[b]	CURR*TIME*AGE
(n=643)	≤18.6	131.00**	130.31**	131.18**	0.173 (0.744)**	0.816**[c]	(p=0.019)
(R^2=0.088)		(102)	(165)	(67)			RACE (p=0.012)
	>18.6	128.70**	130.68**	132.62**	0.512 (0.680)**	0.452**[c]	PACKYR (p=0.063)
		(68)	(154)	(87)			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)
					DXCAT*DIFCORT (p=0.036)
Unknown	300	Unknown vs. Background	****	****	RACE (p=0.110)
Low	172	Low vs. Background	****	****	PACKYR (p=0.102)
High	147	High vs. Background	****	****	CHOL (p=0.010)
					%BFAT (p<0.001)
Total	1,280				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.