TABLE 12-32.

Summary of Dioxin-by-Covariate Interactions from Adjusted Analyses of Cardiovascular Variables

Variable	Assumption	Covariate
Model 1: Ranch Hands - Log_2 (Initial Dioxin)		
Reported/Verified Essential Hypertension	Maximal	DIFCORT
Reported Heart Disease (Excluding Essential Hypertension)	Minimal	RACE
Verified Heart Disease (Excluding Essential Hypertension)	Minimal	RACE
Systolic Blood Pressure (Continuous)	Minimal	AGE,PACKYR
Systolic Blood Pressure (Continuous)	Maximal	PACKYR
Systolic Blood Pressure (Discrete)	Minimal	PERS
ECG: Arrhythmia	Minimal	PERS
Diastolic Blood Pressure (Continuous)	Maximal	PERS
Femoral Pulses	Minimal	PERS
Femoral Pulses	Maximal	PERS
Dorsalis Pedis Pulses	Minimal	DIFCORT
Leg Pulses	Minimal	AGE
Peripheral and All Pulses	Minimal	AGE
Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time		
Systolic Blood Pressure (Continuous)	Minimal	HRTDIS
Systolic Blood Pressure (Continuous)	Maximal	AGE
Systolic Blood Pressure (Discrete)	Minimal	PERS
Systolic Blood Pressure (Discrete)	Maximal	PERS
Heart Sounds	Minimal	HRTDIS,PACKYR
Heart Sounds	Maximal	HRTDIS,PACKYR
ECG: Nonspecific ST- and T-Wave Changes	Maximal	AGE
ECG: Arrhythmia	Maximal	DIFCORT
Femoral Pulses	Maximal	%BFAT,DIFCORT
Popliteal Pulses	Minimal	HRTDIS
Popliteal Pulses	Maximal	PACKYR
Leg Pulses	Minimal	PACKYR
Peripheral and All Pulses	Minimal	PACKYR

TABLE 12-32. (Continued)

Summary of Dioxin-by-Covariate Interactions from Adjusted Analyses of Cardiovascular Variables

Variable	Assumption	Covariate
Model 3: Ranch Hands and Comparisons by Current Dioxin Category		
Reported/Verified Essential Hypertension	- -	AGE
Reported/Verified Myocardial Infarction	- -	DIFCORT
Systolic Blood Pressure (Continuous)	- -	AGE
Systolic Blood Pressure (Discrete)	- -	AGE,DIFCORT
ECG: Bradycardia	- -	RACE
Diastolic Blood Pressure (Continuous)	- -	PERS,HRTDIS
Funduscopic Examination	- -	DIFCORT
Femoral Pulses	- -	PERS

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the unadjusted and adjusted analyses of the questionnaire variables did not display any significant associations with initial dioxin. The unadjusted maximal analyses detected significant negative associations with initial dioxin for reported and verified heart disease (Table 12-29: p=0.007 and p=0.006, respectively) and a marginally significant positive association for reported/verified essential hypertension. Under the maximal assumption, the adjusted analyses detected a marginally significant negative association between initial dioxin and reported heart disease and a significant negative association for verified heart disease (Table 12-29: p=0.044). In addition, the adjusted maximal analysis of reported/verified essential hypertension detected a significant initial dioxin-by-differential cortisol response interaction. Stratified analyses of this interaction revealed no significant results. There were also initial dioxin-by-race interactions found in the minimal analyses of both reported and verified heart disease. These interactions exhibited significant negative associations between initial dioxin and heart disease for Blacks and nonsignificant negative associations between initial dioxin and heart disease for non-Blacks. After deletion of all three of these interactions from the adjusted models, the analyses were nonsignificant.

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

The unadjusted minimal analyses of the questionnaire variables did not reveal any significant results; however, the associations of current dioxin with heart disease and myocardial infarction were negative within both time since tour strata. Under the maximal assumption, the interactions between current dioxin and time since tour were also nonsignificant. The maximal unadjusted analyses of both reported and verified heart disease detected marginally significant negative associations with current dioxin for Ranch Hands with later tours and significant negative associations with current dioxin for Ranch Hands with early tours (Table 12-30: p=0.015 and p=0.013, respectively).

Similar to the unadjusted results, the minimal analyses of the questionnaire variables remained nonsignificant after adjustment for covariate information. The inclusion of covariates in the maximal model caused the negative associations between current dioxin and both reported and verified heart disease to become nonsignificant for Ranch Hands with 18.6 years or less since tour and marginally significant for Ranch Hands with more than 18.6 years since tour. Also, for Ranch Hands with 18.6 years or less since tour, the maximal adjusted analysis of reported/verified myocardial infarction detected a marginally significant positive association with current dioxin.

In addition, after removing percent body fat from the maximal analysis of reported/verified essential hypertension, the positive association with current dioxin became significant for Ranch Hands with later tours (Table 12-30: p=0.023).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis of the questionnaire variables detected significant differences among the four current dioxin categories for reported/verified essential hypertension (Table 12-31: p=0.043) and reported and verified heart disease excluding essential hypertension (p=0.003 and p=0.002). The Ranch Hands in the unknown category had a significantly higher reported incidence of heart disease (p=0.047) and a marginally higher verified incidence of

heart disease than the Comparisons in the background category. Also, the Ranch Hands in the high current dioxin category had significantly lower reported and verified incidence of heart disease than the Comparisons in the background category (p=0.010 and p=0.007, respectively). In addition, in the unadjusted analysis of reported/verified myocardial infarction, the overall contrast of the four current dioxin categories was marginally significant.

After adjusting for covariate information, the overall contrast of the four current dioxin categories remained significant for reported and verified heart disease (Table 12-31: p=0.024 and p=0.021, respectively). However, the contrast of the Ranch Hands in the unknown category versus the Comparisons in the background category became marginally significant. Similarly, in the adjusted analyses, the Ranch Hands in the high category had only a marginally lower risk of reported heart disease and a significantly lower risk of verified heart disease (p=0.049) than the Comparisons in the background category.

The adjusted analysis of reported/verified essential hypertension revealed a significant interaction between categorized current dioxin and age, and similarly, the analysis of reported/verified myocardial infarction detected a significant interaction between categorized current dioxin and differential cortisol response. Stratified results did not indicate a dioxin effect for either variable. After deletion of the interaction, the analysis of reported/verified essential hypertension no longer found a significant difference among the four current dioxin categories. The contrast of the Ranch Hands in the high category versus the Comparisons in the background category became marginally significant. However, after excluding percent body fat and the categorized current dioxin-by-age interaction from the model, the simultaneous contrast of the incidence of essential hypertension of the four current dioxin categories was significant (Table 12-31: p=0.002). Also, the Ranch Hands in the high current dioxin category had a significantly higher risk of essential hypertension than the Comparisons in the background category (p=0.005).

Physical Examination: Central Cardiac Function Variables

Variables analyzed in the evaluation of the central cardiac function included systolic blood pressure, heart sounds, and seven conditions associated with the ECG (overall ECG reading, RBBB, LBBB, nonspecific ST- and T-wave changes, bradycardia, arrhythmia, and other diagnoses). However, there were only three Comparisons and one Ranch Hand diagnosed with LBBB; thus, relative risks, confidence intervals, and p-values were not presented. There were no Ranch Hands and only one Comparison with tachycardia; consequently, no analyses were performed on this cardiovascular endpoint.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted initial dioxin analyses of the central cardiac function variables, only one variable displayed a marginally significant association with initial dioxin under either assumption. The unadjusted analysis of bradycardia detected a marginally significant negative association with initial dioxin under the maximal assumption.

After adjusting for covariate information, the maximal analysis of bradycardia remained marginally significant. Also, the adjusted analyses found significant initial dioxin-by-covariate interactions for systolic blood pressure (both continuous and discrete) and arrhythmia (Table 12-32). The stratified analysis of the interactions for systolic blood

pressure in its continuous form did not exhibit a significant positive association with initial dioxin. The results of the minimal and maximal analyses of systolic blood pressure in its continuous form remained nonsignificant after deletion of the interactions from the model. However, after further deletion of cholesterol and percent body fat, the maximal analysis detected a significant positive association between systolic blood pressure and initial dioxin (Table 12-29: p=0.049).

For discretized systolic blood pressure under the minimal assumption, the stratified analyses of the initial dioxin-by-personality type interaction found a significant decreasing association between the prevalence of abnormally high systolic blood pressure and initial dioxin for Ranch Hands with type A personalities. In contrast, for type B Ranch Hands, there was a nonsignificant positive association with initial dioxin. After the deletion of this interaction, the results were nonsignificant.

An interaction between initial dioxin and personality type was significant for the minimal analysis of arrhythmia. There was a significant positive association between initial dioxin and arrhythmia for type A Ranch Hands and a nonsignificant positive association for type B Ranch Hands. After deletion of this interaction, the minimal adjusted analysis of arrhythmia detected a marginally significant positive association with initial dioxin.

The longitudinal analyses of the minimal and maximal cohorts detected significant negative associations between the percentage of Ranch Hands having an abnormal ECG reading at the 1987 examination and initial dioxin (p=0.014 and p=0.041, respectively).

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

The association between current dioxin and the central cardiac function variables did not differ significantly between time since tour strata for most unadjusted analyses. Under the minimal assumption, the current dioxin-by-time interaction was not significant for any analyses. However, in the unadjusted analysis of Ranch Hands with early tours, the variable of other ECG diagnoses was negatively associated with current dioxin (Table 12-30: p=0.048). Under the maximal assumption, the current dioxin-by-time since tour interaction was marginally significant in the unadjusted analysis of bradycardia, which also displayed a marginally significant negative association with current dioxin for Ranch Hands with more than 18.6 years since their tour. Also, the unadjusted maximal analyses of arrhythmia and other ECG diagnoses detected significant interactions between current dioxin and time (p=0.032 and p=0.040, respectively). These analyses revealed a marginally significant positive association between current dioxin and arrhythmia for Ranch Hands with later tours and a significant negative association between the overall ECG findings and current dioxin for Ranch Hands with early tours (p=0.011).

The adjusted analysis of the minimal cohort was similar to the corresponding unadjusted analysis. There were no significant current dioxin-by-time since tour interactions for the minimal cohort, but for Ranch Hands with 18.6 years or less since their tour, there was a marginally significant positive association between current dioxin and the overall ECG diagnoses and a significant positive association between current dioxin and arrhythmia (Table 12-30: p=0.017).

For the adjusted analyses under the maximal assumption, the current dioxin-by-time since tour interaction was marginally significant for bradycardia and significant for other ECG diagnoses (Table 12-30: p=0.026). The associations with current dioxin for Ranch Hands with early tours exhibited a similar significance for these two variables (bradycardia: marginally significant negative association; other ECG diagnoses: significant negative association, p=0.046). Also, after deletion of a current dioxin-by-time-by-differential cortisol-response interaction, the maximal adjusted analysis displayed a significant difference in the associations between current dioxin and arrhythmia (p=0.034). There was a positive association between arrhythmia and current dioxin (p=0.018) for Ranch Hands with late tours.

For four of the central cardiac function variables, there were significant interactions among current dioxin, time since tour, and one or more covariates (Table 12-32). The covariates involved in these interactions were age, lifetime cigarette smoking history, personality type, differential cortisol response, and family history of heart disease. All results, except those mentioned above for arrhythmia, were nonsignificant after the deletion of the interactions from the adjusted models.

The longitudinal analysis of the 1987 ECG conditioned on participants with normal ECG readings in 1982 did not detect significant current dioxin-by-time interactions for either the minimal or the maximal cohort. However, there were significant negative associations between current dioxin and the overall ECG reading for Ranch Hands with more than 18.6 years since tour (p=0.013 and p=0.025, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted and adjusted analyses of the central cardiac function variables and categorized current dioxin generally were not significant. In the unadjusted analysis, other ECG diagnoses was the only variable with a significant overall contrast of the four current dioxin categories (Table 12-31: p=0.024). Also, the Ranch Hands in the high current dioxin category had a significantly lower risk of other abnormal ECG diagnoses than the Comparisons in the background category (p=0.007). All other unadjusted results were nonsignificant.

In the adjusted analyses of the central cardiac function variables, the overall contrasts of the four current dioxin categories were not significant except for systolic blood pressure in its continuous form after the deletion of a categorized current dioxin-by-age interaction, cholesterol, and percent body fat (Table 12-31: p=0.012). Also, after these deletions, the Ranch Hands in the unknown current dioxin category had a marginally lower mean systolic blood pressure than the Comparisons in the background category and the Ranch Hands in the high category had a significantly higher mean systolic blood pressure than the Comparisons in the background category (p=0.019).

In the adjusted analyses, the Ranch Hands in the unknown current dioxin category had a marginally lower risk of abnormal overall ECG diagnoses than the Comparisons in the background category. Also, the Ranch Hands in the high current dioxin category had a marginally lower risk of bradycardia (after the deletion of a categorized current dioxin-by-race interaction and percent body fat) and a significantly lower risk of other abnormal ECG

diagnoses than the Comparisons in the background category (Table 12-31: p=0.036). In contrast, the Ranch Hands in the high current dioxin category had a marginally higher risk of arrhythmia than the Comparisons in the background category.

The adjusted analyses revealed significant categorized current dioxin-by-covariate interactions for systolic blood pressure (continuous and discrete) and bradycardia (Table 12-32). Stratified analyses of these interactions did not display any strong dioxin effects for these variables. After deletion of these interactions, the adjusted results generally remained nonsignificant.

In the longitudinal analysis, the percentages of participants who had abnormal ECG readings in 1987 did not differ significantly among the four current dioxin categories. However, the percentage of Comparisons in the background category who had abnormal ECG readings in 1987 was marginally higher than the corresponding percentage of Ranch Hands in the high category (p=0.094).

Physical Examination: Peripheral Vascular Function Variables

The peripheral vascular function was assessed during the cardiovascular examination by the diastolic blood pressure; funduscopic examination of small vessels of the retina; the presence or absence of carotid bruits; and manual palpation of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. In addition, three pulse indices were constructed from the above pulse measurements: leg pulses (femoral, popliteal, dorsalis pedis, and posterior tibial pulses), peripheral pulses (radial and leg pulses), and all pulses (peripheral and carotid pulses). Each of these indices was considered normal if all components were normal and abnormal if one or more pulses were abnormal. There were only two Ranch Hands and four Comparisons with absent radial pulses; thus, relative risks, confidence intervals, and p-values were not presented for this endpoint.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analyses of the peripheral vascular function variables, there were no significant results under the minimal assumption. However, the maximal unadjusted analyses detected marginally significant positive association with current dioxin for dorsalis pedis, leg, peripheral, and all pulses. These marginal associations became significant after adjustment for covariate information (Table 12-29: p=0.041, p=0.021, and p=0.025, respectively). Similarly, under the maximal assumption, the adjusted analysis displayed a marginally significant positive association between initial dioxin and posterior tibial pulses, which became nonsignificant after the deletion of percent body fat from the model.

The adjusted maximal analysis displayed a significant interaction between initial dioxin and personality type for diastolic blood pressure in its continuous form. Stratified analyses of this interaction revealed a marginally significant negative association with initial dioxin for type A Ranch Hands and a significant positive association for type B Ranch Hands (Table 12-29: p=0.015). The adjusted analyses (minimal and maximal) of femoral pulses also displayed significant interactions between initial dioxin and personality type; however, these interactions may have been affected by the sparse number of Ranch Hands with absent femoral pulses. The interactions between initial dioxin and age in the minimal adjusted analyses of leg, peripheral, and all pulses displayed nonsignificant negative associations with

initial dioxin for younger Ranch Hands, but a significant positive association for older Ranch Hands. There was also an interaction between initial dioxin and differential cortisol response for the minimal analysis of dorsalis pedis pulses, which did not show any significant dioxin effects.

After deletion of these initial dioxin-by-covariate interactions from the adjusted models, the results were nonsignificant.

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

In the minimal and the maximal unadjusted analyses of the peripheral vascular function variables, the associations with current dioxin did not differ significantly between the time since tour strata. In general, the relative risks were lower for Ranch Hands with earlier tours than for Ranch Hands with later tours.

In the adjusted analyses, the interactions between current dioxin and time since tour were nonsignificant for both the minimal and the maximal cohorts. However, under the minimal assumption, the adjusted analysis detected a marginally significant positive association between current dioxin and dorsalis pedis pulses for Ranch Hands with 18.6 years or less since tour, which became significant under the maximal assumption (Table 12-30: $p=0.048$). The maximal adjusted analysis of Ranch Hands with 18.6 years or less since tour also detected marginally significant positive associations with current dioxin for abnormal posterior tibial pulses and the leg, peripheral, and all pulses indices. However, after deletion of percent body fat from the adjusted maximal model, the association between current dioxin and abnormal posterior tibial pulses was no longer marginally significant.

The adjusted maximal analysis of femoral pulses revealed significant interactions among current dioxin, time since tour, percent body fat, and differential cortisol response, which were in part caused by the small number of Ranch Hands with abnormal femoral pulses. The analyses of popliteal pulses and the three pulse indices (leg, peripheral, all) detected significant interactions with lifetime cigarette smoking history. Stratified analyses of these interactions displayed a positive association between current dioxin and the dependent variable for heavy smokers with later tours and a negative association for heavy smokers with earlier tours. After deletion of these interactions, the analyses were generally nonsignificant.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analyses of categorized current dioxin and the peripheral vascular function variables generally were nonsignificant. The only variables with significant overall contrasts of the four current dioxin categories were diastolic blood pressure in its continuous form (Table 12-31: $p=0.017$), posterior tibial pulses ($p<0.001$) and the leg pulses index (marginal significance). The contrasts of the Ranch Hands in the unknown current dioxin category and in the high category (except for diastolic blood pressure in its continuous form) versus the Comparisons in the background category were all nonsignificant but generally in a positive direction. However, Ranch Hands in the low current dioxin category had a significantly higher mean diastolic blood pressure ($p=0.028$) and higher risks of abnormal dorsalis pedis pulses (marginal significance), posterior tibial pulses ($p=0.003$), leg pulses ($p=0.010$), peripheral pulses ($p=0.016$), and all pulses ($p=0.019$) than the Comparisons in the

background category. Ranch Hands in the high category also had a marginally higher mean diastolic blood pressure than the Comparisons in the background category.

The adjusted analyses of categorized current dioxin and the peripheral vascular function variables detected a larger number of differences among the four current dioxin categories than the unadjusted analyses (Table 12-31). These analyses revealed significant overall differences among the four current dioxin categories for posterior tibial pulses ($p<0.001$), leg pulses ($p=0.020$), peripheral pulses ($p=0.017$), and all pulses ($p=0.021$). Also, after deletion of categorized current dioxin, personality type, and family history of heart disease interactions from the analysis of diastolic blood pressure in its continuous form, the overall contrast of the four current dioxin categories was marginally significant. In this same analysis, the further exclusion of cholesterol and percent body fat caused the overall contrast to become significant ($p=0.002$). Similarly, the deletion of cholesterol from the adjusted analysis of dorsalis pedis pulses caused the overall contrast of the four current dioxin categories to become marginally significant.

Consistent with the unadjusted results, the adjusted analyses did not detect any significant differences in the peripheral vascular function variables between the Ranch Hands in the unknown current dioxin category and the Comparisons in the background category (Table 12-31). However, the Ranch Hands in the low current dioxin category had a significantly higher mean diastolic blood pressure ($p=0.032$ after deletion of interactions) and significantly higher risks of abnormal posterior tibial pulses ($p<0.001$), leg pulses ($p=0.005$), peripheral pulses ($p=0.007$), and all pulses ($p=0.008$) than the Comparisons in the background category. These Ranch Hands also had marginally higher risks of abnormal femoral pulses (after deletion of a categorized current dioxin-by-personality type interaction) and dorsalis pedis pulses.

The Ranch Hands in the high current dioxin category had significantly higher risks of abnormal femoral pulses (Table 12-31: $p=0.049$, after deletion of categorized current dioxin-by-personality type interaction), leg pulses ($p=0.047$), peripheral pulses ($p=0.033$), and all pulses ($p=0.035$). After deletion of interactions, the adjusted analysis also revealed a marginally higher mean diastolic blood pressure for Ranch Hands in the high current dioxin category than for Comparisons in the background category; this contrast became significant after the deletion of cholesterol and percent body fat from the model ($p=0.017$). Similarly, the Ranch Hands in the high current dioxin category had a marginally higher risk of abnormal dorsalis pedis pulses than the Comparisons; this contrast also became significant after the deletion of cholesterol from the adjusted model ($p=0.029$).

The analyses of the peripheral vascular function variables discovered interactions between categorized current dioxin and personality type, differential cortisol response, and family history of heart disease (Table 12-32). The stratified analyses of these interactions failed to detect any significant dioxin effects or covariate trends. However, these interactions may have been affected by the sparse number of abnormalities of several of the peripheral vascular function variables. Results after the deletion of these interactions were nonsignificant unless otherwise discussed above.

CONCLUSION

The cardiovascular evaluation found a marginal association between initial dioxin and a decrease in the incidence of reported heart disease and a significant negative association with verified heart disease in the maximal cohort. Analyses displayed similar marginally significant negative associations only for Ranch Hands with early tours of duty in Vietnam under the maximal assumption. In addition, the analyses of categorized current dioxin also indicated a decreased incidence of verified heart disease for Ranch Hands with the highest current dioxin levels relative to the Comparisons with background levels. These Ranch Hands also displayed an increased incidence of essential hypertension (after removing percent body fat and cholesterol from the model).

In general, the analyses of the central cardiac function variables were not positively associated with dioxin. By continuous analysis, Ranch Hands under the maximal assumption exhibited a significant positive association between initial serum levels and systolic blood pressure when percent body fat was not considered. This finding was not significant after adjustment for percent body fat, and in no models was initial dioxin associated significantly with abnormally high levels of systolic blood pressure.

The analyses of the peripheral vascular function variables displayed significantly higher mean levels of diastolic blood pressure for Ranch Hands in the low and high categories than Comparisons (without adjustment for percent body fat). Similar to the analysis of systolic blood pressure, the discretized analysis of diastolic blood pressure did not display a significant association with dioxin within the low and high current dioxin categories. Ranch Hands generally exhibited a significant or marginally significant higher risk of absent femoral, dorsalis pedis, and posterior tibial pulses relative to the Comparisons. Due to the high correlation of the leg pulse variables and the composite pulse indices, it is not surprising that the leg, peripheral, and all pulse indices displayed a significant positive association with dioxin. These pulses will be further evaluated at the 1992 physical examination. These observations could represent a subclinical effect and emphasize the importance of continued followup and evaluation in subsequent examination phases of the study.

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

In general, the development of nondiabetes-related cardiovascular disease does not appear to be associated positively with dioxin; however, there were significant associations between dioxin and peripheral pulse deficits and systolic blood pressure. The cardiovascular assessment was primarily based on nondiabetics only. Additional analyses based on diabetics only were done for myocardial infarction and leg pulses; no significant results were found in these analyses.

CHAPTER 12

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CHAPTER 13

HEMATOLOGIC ASSESSMENT

INTRODUCTION

Background

Experiments in laboratory animals have demonstrated that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is directly toxic to the hematopoietic system in several species. In one study, TCDD administered in low doses to monkeys resulted in elevated neutrophil counts while higher doses were associated with lympho- and thrombocytopenia (1). A decrease in overall cellularity and an increase in the myeloid-erythroid ratio were noted in approximately half of the sternal bone marrow samples examined at the conclusion of the experiment.

Other animal studies have shown that the toxic effects of TCDD on the hematopoietic system vary depending on the dose employed and the species examined. In many reports it is difficult to distinguish primary effects from those occurring secondary to systemic toxicity. In one rat study using gavage doses of TCDD varying from 0.001 to 1.0 μg/kg, depressed red blood cell counts and packed cell volumes were noted in the high-dose group (2). In another rat experiment, elevated erythrocyte, reticulocyte, and neutrophil counts were noted with reduction in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelet counts, and clot retraction times—effects the authors felt could be attributed to systemic toxicity with terminal dehydration (3). In another multispecies study, mice and guinea pigs were found to have dose-dependent reductions in leukocytes with relative lymphocytopenia within 1 week of TCDD administration while thrombocytopenia and hemoconcentration were found in rats (4).

More recent animal research relevant to the hematopoietic system has focused on the altered cellular differentiation associated with TCDD toxicity. In mice, progenitor cells were suppressed following exposure to TCDD in doses as low as 1.0 μg/kg of body weight and in vitro studies demonstrated that myelotoxicity occurs by a direct inhibition of proliferating stem cells (5). A subsequent study from the same laboratory demonstrated a direct effect of TCDD on cultured lymphocytes resulting in a selective inhibition of B-cell differentiation into antibody-secretive cells (6). In these and other studies (7), the authors cite evidence for the role of the aryl hydroxylase (Ah) receptor in mediating these myelo- and lymphotoxic effects.

In general, human observational studies have shown fewer and less consistent hematologic findings than the structured animal experiments. A case report of 2,4-D intoxication with marked neurological findings described transient bone marrow depression with peripheral leukopenia and granulocytopenia (8). In two industrial accidents involving significant contamination with TCDD associated with chloracne, temporary depression of peripheral leukocyte and lymphocyte formation was observed (9, 10).

Several contemporary human morbidity studies have included routine, complete blood counts in examination protocols (11, 12). A clinical epidemiologic study was conducted 30 years after the Nitro, West Virginia, trichlorophenol explosion. The study compared 204

highly exposed employees (86% of whom had developed chloracne) with 163 who were not exposed (12). No significant differences were found in the standard hematologic indices.

Numerous studies have been conducted on cohorts exposed to TCDD by environmental contamination of the soil in the Quail Run (13, 14, 15) and Times Beach (16) residential areas of Missouri. With one exception, no differences were found in any of the hematologic parameters examined. In the Times Beach study, a statistically significant increase in the mean platelet count was noted in the exposed cohort relative to the unexposed, but the difference (281,927/mm^3 versus 249,061/mm^3) was not clinically significant. A more recent study, the first to report clinical indices in relation to tissue levels of dioxin (17), found no abnormalities in the complete blood count related to the body burden of TCDD.

More detailed summaries of the pertinent scientific literature for the hematologic assessment can be found in the report of the previous analyses of the 1987 examination data (18).

Summary of Previous Analyses of the 1987 Examination Data

The hematologic status of the Ranch Hand and Comparison groups was assessed by the examination of eight variables: red blood cell count (RBC), white blood cell count (WBC), hemoglobin, hematocrit, MCV, MCH, mean corpuscular hemoglobin concentration (MCHC), and platelet count. There were no statistically significant differences between the two groups for RBC count, hemoglobin, hematocrit, MCV, MCH, and MCHC, in analyses either unadjusted or adjusted for the covariates of age, race, occupation, current cigarette smoking, and lifetime cigarette smoking history. For WBC count, the mean level was significantly greater in the Ranch Hands than in the Comparisons. The difference was not statistically significant after adjustment for covariates, nor were significant differences detected in the percentage of individuals with abnormal values.

Mean platelet counts were also significantly greater in the Ranch Hands than in the Comparisons, as was the percentage of individuals with abnormally high values. While these differences remained significant after adjustment for covariates, no platelet count was above 595,000/mm^3. Longitudinal analyses detected a significantly greater decrease in the mean platelet count from Baseline to the 1987 examination in the Ranch Hands than in the Comparisons, despite the higher overall mean count.

Parameters of the Hematologic Assessment

Dependent Variables

The analysis of the hematologic assessment consisted of data from the laboratory examination only. No questionnaire or physical examination data were analyzed.

Laboratory Examination Data

Nine hematology variables measured at the laboratory examination were analyzed—RBC count (million/mm^3), WBC count (thousand/mm^3), hemoglobin (gm/dl), hematocrit (percent), MCV (cubic micra), MCH (micromicrogram), MCHC (gm/dl), platelet count (thousand/mm^3), and prothrombin time (seconds). These variables were determined by routine hematologic procedures. All dependent variables were analyzed in both the discrete

and continuous forms except for MCHC. MCHC was analyzed only in the continuous form since abnormal values (<31 gm/dl or >37 gm/dl) were not found in any participants.

For the discrete analyses, RBC count, hematocrit, MCV, MCH, platelet count, and prothrombin time were initially coded as abnormal low, normal, and abnormal high. However, the frequencies for these variables showed a sparseness of data in the abnormal high RBC count and hematocrit categories, and in the abnormal low MCV, MCH, and platelet count categories. Eighteen participants (7 Ranch Hands and 11 Comparisons) had abnormally high RBC counts and only 3 participants (2 Ranch Hands and 1 Comparison) had abnormally high hematocrit levels. Abnormally low MCV and MCH levels were found in only 19 participants (8 Ranch Hands and 11 Comparisons) and 9 participants (5 Ranch Hands and 4 Comparisons), respectively. Only four Ranch Hands and two Comparisons had an abnormally low platelet count. No participants had an abnormally low prothrombin time (<10.4 seconds). Because of these sparse frequencies, these categories were combined with the normal categories. Thus, RBC count and hematocrit were classified as normal/high or abnormal low, and MCV, MCH, platelet count, and prothrombin time were classified as normal/low or abnormal high.

The Scripps Clinic and Research Foundation (SCRF) laboratory coefficients of variation for these variables met or exceeded requirements due to the precision of the Coulter S Plus® automated instrument, in conjunction with fast initial response cumulative sum quality control techniques. The SCRF laboratory normal values varied to some extent from the Kelsey-Seybold Clinic norms used at the Baseline examination (see page XVI-3-1, Baseline report). The SCRF laboratory normal values for all variables, except MCHC, are given in Table 13-1. Although MCHC was not analyzed in discrete form, an MCHC reading between 31.0 gm/dl and 37.0 gm/dl is considered normal. An MCHC reading below 31.0 gm/dl is considered abnormally low, and a reading above 37.0 gm/dl is considered abnormally high.

A natural logarithm transformation was applied to the WBC count and prothrombin time data for the continuous analyses. Participants with a fever (body temperature greater than or equal to 100°F) at the time of the examination were excluded from the analysis of all variables except prothrombin time. Participants who were taking an anticoagulant (Coumadin®) or aspirin at the time of the examination or who tested positive for the human immunosuppressant virus (HIV) were excluded from the analysis of prothrombin time.

Covariates

Age, race, current level of cigarette smoking (cigarettes/day), and lifetime cigarette smoking history (pack-years) were used as candidate covariates in adjusted statistical analyses evaluating the hematologic dependent variables. Current alcohol use (drinks/day) and lifetime alcohol history (drink-years) were also used as candidate covariates in adjusted analyses of prothrombin time. For the analyses of RBC count, hematocrit, MCV, MCH, platelet count, and prothrombin time in the discrete form, age, current cigarette smoking, and lifetime cigarette smoking history were used in their continuous form. Current alcohol use and lifetime alcohol history were also used in continuous form for the analyses of prothrombin time. For the analyses of WBC count and hemoglobin in the discrete form, age and the two cigarette smoking covariates were used in their discrete form. In continuous analyses, age, the two cigarette smoking variables, and the two alcohol variables (for the analyses of prothrombin time) were used in the continuous form.

TABLE 13-1.

Statistical Analysis for the Hematologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Red Blood Cell Count (RBC) (million/mm^3)	LAB	D/C	Abnormal Low: <4.3 Normal/High: ≥4.3	AGE,RACE, CSMOK,PACKYR	U:LR,GLM A:LR,GLM
White Blood Cell Count (WBC) (thousand/mm^3)	LAB	D/C	Abnormal Low: <4.5 Normal: 4.5-11.0 Abnormal High: >11.0	AGE,RACE, CSMOK,PACKYR	U:LL,GLM A:LL,GLM
Hemoglobin (gm/dl)	LAB	D/C	Abnormal Low: <13.9 Normal: 13.9-18.0 Abnormal High: >18.0	AGE,RACE, CSMOK,PACKYR	U:LL,GLM A:LL,GLM
Hematocrit (percent)	LAB	D/C	Abnormal Low: <39.0 Normal/High: ≥39.0	AGE,RACE, CSMOK,PACKYR	U:LR,GLM A;LR,GLM
Mean Corpuscular Volume (MCV) (cubic micra)	LAB	D/C	Normal/Low: ≤97.0 Abnormal High: >97.0	AGE,RACE, CSMOK,PACKYR	U:LR,GLM A:LR,GLM L:GLM
Mean Corpuscular Hemoglobin (MCH) (micromicrogram)	LAB	D/C	Normal/Low: ≤34.0 Abnormal High: >34.0	AGE,RACE, CSMOK,PACKYR	U:LR,GLM A:LR,GLM L:GLM

TABLE 13-1. (Continued)

Statistical Analysis for the Hematologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Mean Corpuscular Hemoglobin Concentration (MCHC) (gm/dl)	LAB	C	- -	AGE,RACE, CSMOK,PACKYR	U:GLM A:GLM
Platelet Count (thousand/mm^3)	LAB	D/C	Normal/Low: ≤400 Abnormal High: >400	AGE,RACE, CSMOK,PACKYR	U:LR,GLM A:LR,GLM L:GLM
Prothrombin Time (seconds)	LAB	D/C	Normal/Low: ≤13.2 Abnormal High: >13.2	AGE,RACE, CSMOK,PACKYR, ALC,DRKYR	U:LR,GLM A:LR,GLM

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	D/C	0-Never 0-Former >0-20 >20

TABLE 13-1. (Continued)

Statistical Analysis for the Hematologic Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
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	--

Abbreviations

Data Source: LAB--1987 SCRF laboratory results
MIL--Air Force military records
Q-SR--1987 NORC 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: GLM--General linear models analysis
LL--Log-linear models analysis
LR--Logistic regression analysis

Relation to Baseline, 1985, and 1987 Studies

Eight of the variables analyzed in this report (RBC count, WBC count, hemoglobin, hematocrit, MCV, MCH, MCHC, and platelet count) were also analyzed in the Baseline, 1985, and 1987 studies. Prothrombin time was not analyzed in the Baseline, 1985, or 1987 studies.

Statistical Methods

Table 13-1 summarizes the statistical analyses performed for the hematologic assessment. The first part of this table describes the dependent variables analyzed. The second part of this table provides a further description of the candidate covariates examined. Abbreviations are used extensively in the body of the table and are defined in footnotes. Chapter 4, Statistical Methods, describes the basic statistical analysis methods used in the hematologic assessment. Table 13-2 provides the number of participants excluded as well as the number of participants with missing data for platelet count, current alcohol use, and lifetime alcohol history.

Appendix L-1 contains graphic displays of hematology dependent variables versus initial dioxin for the minimal and maximal Ranch Hand cohorts, and hematology dependent variables versus current dioxin for Ranch Hands and Comparisons. Appendix L-2 presents graphics for dioxin-by-covariate interactions determined by various statistical models. A guide to assist in interpreting the graphics is found in Chapter 4.

Three statistical models were used to examine the association between a hematology 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 hematology 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 (18). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion of the models.

RESULTS

Exposure Analysis

Questionnaire Variables

Red Blood Cell Count (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analysis under the minimal assumption exhibited a nonsignificant association between RBC count and initial dioxin (Table 13-3 [a]: p=0.442). There was,

TABLE 13-2.

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

Variable	Variable Use	Assumption (Ranch Hands Only) Minimal	Assumption (Ranch Hands Only) Maximal	Categorized Current Dioxin Ranch Hand	Categorized Current Dioxin Comparison
Platelet Count	DEP	1	1	0	0
Temperature ≥100°F at physical examination	EXC	1	1	1	3
Taking Anticoagulant (Coumadin®)	EXC	1	1	1	0
Taking Aspirin	EXC	0	0	0	1
HIV Positive	EXC	1	1	1	0
Current Alcohol Use	COV	3	5	5	0
Lifetime Alcohol History	COV	6	9	9	2

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

TABLE 13-3.

Analysis of Red Blood Cell Count (million/mm^3) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal	Low	130	4.935	0.0105 (0.0136)	0.442
(n=520)	Medium	259	4.990		
(R^2=0.001)	High	131	4.955		
b) Maximal	Low	185	4.908	0.0194 (0.0098)	0.048
(n=741)	Medium	370	4.963		
(R^2=0.005)	High	186	4.976		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c) Minimal	Low	130	4.946	0.0034 (0.0140)	0.808	AGE (p=0.035)
(n=520)	Medium	259	4.992			
(R^2=0.010)	High	131	4.942			
d) Maximal	Low	185	5.002	0.0162 (0.0099)	0.103	AGE (p=0.052)
(n=741)	Medium	370	5.050			RACE*CSMOK
(R^2=0.039)	High	186	5.057			(p=0.030)

[a]Slope and standard error based on red blood cell count versus log_2 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 13-3. (Continued)

Analysis of Red Blood Cell Count (million/mm^3) (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						0.710[b]
(n=520)	≤18.6	4.975	4.999	4.983	0.0110 (0.0222)	0.621[c]
(R^2=0.006)		(72)	(128)	(54)		
	>18.6	4.897	4.965	4.955	0.0216 (0.0182)	0.234[c]
		(58)	(131)	(77)		
f) Maximal						0.208[b]
(n=741)	≤18.6	4.891	4.963	5.010	0.0343 (0.0153)	0.025[c]
(R^2=0.007)		(106)	(191)	(83)		
	>18.6	4.965	4.929	4.980	0.0086 (0.0135)	0.525[c]
		(79)	(178)	(104)		

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						0.660[b]	AGE (p=0.078)
(n=520)	≤18.6	4.983	4.994	4.960	0.0013 (0.0228)	0.953[c]	
(R^2=0.012)		(72)	(128)	(54)			
	>18.6	4.916	4.971	4.949	0.0139 (0.0186)	0.455[c]	
		(58)	(131)	(77)			
h) Maximal						0.213**[b]	CURR*TIME*AGE
(n=741)	≤18.6	5.015**	5.082**	5.116**	0.0283 (0.0154)**	0.067**[c]	(p=0.038)
(R^2=0.049)		(106)	(191)	(83)			CSMOK (p=0.009)
	>18.6	5.102**	5.050**	5.092**	0.0031 (0.0136)**	0.818**[c]	RACE*PACKYR
		(79)	(178)	(104)			(p=0.039)

[a]Slope and standard error based on red blood cell count versus log_2 dioxin.

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

[c]Test of significance for slope different from 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 13-3. (Continued)

Analysis of Red Blood Cell Count (million/mm^3) (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	783	4.960	All Categories		0.147
Unknown	345	4.918	Unknown vs. Background	-0.041 (-0.089,0.006)	0.088
Low	195	4.959	Low vs. Background	-0.001 (-0.060,0.058)	0.983
High	187	4.993	High vs. Background	0.033 (-0.026,0.093)	0.274
Total	1,510		(R^2=0.004)		

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	783	5.031	All Categories		0.440	AGE (p<0.001)
						RACE (p<0.001)
Unknown	345	4.994	Unknown vs. Background	-0.036 (-0.083,0.010)	0.128	CSMOK (p<0.001)
Low	195	5.025	Low vs. Background	-0.006 (-0.063,0.052)	0.842	PACKYR
High	187	5.038	High vs. Background	0.007 (-0.052,0.066)	0.816	(p=0.066)
Total	1,510		(R^2=0.050)			

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.

however, a significant positive association under the maximal assumption (Table 13-3 [b]: p=0.048). The means were 4.908, 4.963, and 4.976 million/mm^3 for the low, medium, and high categories of initial dioxin.

After the model was adjusted for age, the association between RBC count and initial dioxin remained nonsignificant under the minimal assumption (Table 13-3 [c]: p=0.808). Under the maximal assumption, the association became nonsignificant when the model was adjusted for age and the race-by-current cigarette smoking interaction (Table 13-3 [d]: p=0.103).

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

The current dioxin-by-time since tour interaction was not significant in the unadjusted analyses of RBC count under the minimal and maximal assumptions (Table 13-3 [e] and [f]: p=0.710 and p=0.208). There was a significant positive association between RBC count and current dioxin for those Ranch Hands in the maximal cohort whose time since tour did not exceed 18.6 years (Table 13-3 [f]: p=0.025). The means, which were 4.891, 4.963, and 5.010 million/mm^3, increased over the low, medium, and high levels of current dioxin.

In the adjusted minimal analysis the current dioxin-by-time interaction remained nonsignificant (Table 13-3 [g]: p=0.660). In the maximal analysis, there was a significant interaction among current dioxin, time, and age (Table 13-3 [h]: p=0.038). To study this interaction, age was divided into two strata: Ranch Hands who were born in or after 1942 and Ranch Hands who were born before 1942. In the stratum containing the younger Ranch Hands, the current dioxin-by-time interaction was not significant (Appendix Table L-1: p=0.605). However, there was a marginally significant positive association between RBC count and current dioxin when time since tour was less than or equal to 18.6 years (p=0.063). The adjusted means for the low, medium, and high current dioxin levels were 5.018, 5.103, and 5.179 million/mm^3. There was also a significant positive association when time since tour was greater than 18.6 years (p=0.018). The adjusted means in this stratum were 5.116, 5.041, and 5.218 million/mm^3.

In the stratum containing the older Ranch Hands, the current dioxin-by-time interaction was significant (p=0.035). For time less than or equal to 18.6 years, the association was positive, but nonsignificant (p=0.299). For time greater than 18.6 years, there was a significant negative association (p=0.033). The means within this time stratum were 5.102, 5.060, and 4.969 million/mm^3 for the low, medium, and high levels of current dioxin.

After the current dioxin-by-time-by-age interaction was removed from the model in the maximal analysis, there was a nonsignificant interaction between current dioxin and time since tour (Table 13-3 [h]: p=0.213). For those Ranch Hands whose time since tour did not exceed 18.6 years, however, there was a marginally significant positive association between RBC count and current dioxin (p=0.067). The covariates that were retained in this model were age, current cigarette smoking, and the interaction between race and lifetime cigarette smoking history.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast of the four current dioxin categories was not significant in the unadjusted analysis of RBC count (Table 13-3 [i]: p=0.147). However, the mean RBC count for the unknown current dioxin category was marginally lower than the corresponding mean of the background category (p=0.088). The means for the background, unknown, low, and high categories were 4.960, 4.918, 4.959, and 4.993 million/mm^3.

When the RBC count was adjusted for covariates, the overall contrast remained nonsignificant (Table 13-3 [j]: p=0.440) and the difference between the unknown and background categories became nonsignificant (p=0.128). The covariates that were retained in the model were age, race, current cigarette smoking, and lifetime cigarette smoking history.

Red Blood Cell Count (Discrete)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

There was no significant association between abnormally low RBC count and initial dioxin for either the minimal or the maximal assumption in unadjusted analyses (Table 13-4 [a] and [b]: p=0.357 and p=0.453, respectively). After adjusting for covariates, the association remained nonsignificant under both assumptions (Table 13-4 [c] and [d]: p=0.193 and p=0.234, respectively).

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

Under the minimal assumption there was a marginally significant interaction between current dioxin and time since tour in the unadjusted analyses of abnormally low RBC counts (Table 13-4 [e]: p=0.066). For time less than or equal to 18.6 years, the risk of an abnormally low RBC count was less than 1 (Adj. RR=0.29, p=0.232). For time greater than 18.6 years, the risk was greater than 1 (Adj. RR=1.32, p=0.229). However, neither risk was significant. Under the maximal assumption the current dioxin-by-time since tour interaction was also significant (Table 13-4 [f]: p=0.012). For time less than or equal to 18.6 years, the risk of an abnormally low RBC count was 0.47 but was nonsignificant (p=0.110). For time greater than 18.6 years, the risk was 1.42 and was marginally significant (p=0.062). Within this time stratum, the percentages of abnormal low RBC counts in the low, medium, and high current dioxin categories were 1.3, 2.3, and 5.8 percent.

No covariates were retained in the minimal adjusted analysis, thus the results remained unchanged. In the maximal analysis, the current dioxin-by-time interaction remained significant after age was retained in the model (Table 13-4 [h]: p=0.011). The risk of an abnormally low RBC count remained nonsignificant for time less than or equal to 18.6 years (Adj. RR=0.50, p=0.159) and became significant for time greater than 18.6 years (Adj. RR=1.58, p=0.018).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

Both the unadjusted and the adjusted analyses showed no significant differences in the percentage of abnormally low RBC counts among the four current dioxin categories (Table 13-4 [i] and [j]: p=0.725 for the unadjusted analysis; p=0.641 for the adjusted analysis).

TABLE 13-4.

Analysis of Red Blood Cell Count (Discrete)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal Low	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=520)	Low	130	2.3	1.22 (0.81,1.86)	0.357
	Medium	259	1.5		
	High	131	4.6		
b) Maximal (n=741)	Low	185	3.2	1.13 (0.82,1.56)	0.453
	Medium	370	1.6		
	High	186	3.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=520)	1.34 (0.88,2.03)	0.193	AGE (p=0.073)
d) Maximal (n=741)	1.23 (0.88,1.71)	0.234	AGE (p=0.019)

[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 13-4. (Continued)

Analysis of Red Blood Cell Count (Discrete)

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

Assumption	Time (Yrs.)	Percent Abnormal Low/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.066[b]
(n=520)	≤18.6	1.4 (72)	1.6 (128)	0.0 (54)	0.29 (0.04,2.22)	0.232[c]
	>18.6	3.5 (58)	2.3 (131)	6.5 (77)	1.32 (0.84,2.06)	0.229[c]
f) Maximal						0.012[b]
(n=741)	≤18.6	3.8 (106)	1.6 (191)	0.0 (83)	0.47 (0.19,1.19)	0.110[c]
	>18.6	1.3 (79)	2.3 (178)	5.8 (104)	1.42 (0.98,2.06)	0.062[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			0.066[b]	- -
(n=520)	≤18.6	0.29 (0.04,2.22)	0.232[c]	
	>18.6	1.32 (0.84,2.06)	0.229[c]	
h) Maximal			0.011[b]	AGE (p=0.022)
(n=741)	≤18.6	0.50 (0.19,1.32)	0.159[c]	
	>18.6	1.58 (1.08,2.31)	0.018[c]	

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

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

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

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

TABLE 13-4. (Continued)

Analysis of Red Blood Cell Count (Discrete)

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

Current Dioxin Category	n	Percent Abnormal Low	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	3.6	All Categories		0.725
Unknown	345	3.5	Unknown vs. Background	0.97 (0.49,1.93)	0.935
Low	195	2.1	Low vs. Background	0.56 (0.20,1.63)	0.290
High	187	3.2	High vs. Background	0.89 (0.36,2.19)	0.806
Total	1,510				

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	783	All Categories		0.641	AGE (p<0.001) RACE (p=0.071)
Unknown	345	Unknown vs. Background	0.99 (0.49,1.99)	0.977	
Low	195	Low vs. Background	0.57 (0.20,1.66)	0.303	
High	187	High vs. Background	1.26 (0.50,3.16)	0.617	
Total	1,510				

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.

White Blood Cell Count (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

A positive association between WBC count and initial dioxin was marginally significant under the minimal assumption in the unadjusted analysis (Table 13-5 [a]: p=0.071). The means for the low, medium, and high levels of initial dioxin were 6.589, 7.118, and 6.978 thousand/mm^3. Under the maximal assumption, the association was significantly positive (Table 13-5 [b]: p<0.001) with means equal to 6.496, 6.854, and 7.055 thousand/mm^3 for the low, medium, and high initial dioxin levels.

When the model under the minimal assumption was adjusted for covariates, a significant interaction between initial dioxin and race was present (Table 13-5 [c]: p<0.001). Race was then divided into two strata: Black and non-Black. In the Black stratum, there was a significant positive association between WBC count and initial dioxin (Appendix Table L-1: slope=0.1756, p<0.001). The adjusted mean WBC counts were 5.373, 7.346, and 8.016 thousand/mm^3 for the low, medium, and high levels of initial dioxin. In the non-Black stratum, the association was not significant (slope=0.0088, p=0.308). The significant interaction was due to the fact that the Black stratum had a steeper slope than the non-Black stratum.

Under the maximal assumption there was also a significant interaction between initial dioxin and race in the adjusted model (Table 13-5 [d]: p=0.001). There was a significant positive association between WBC count and initial dioxin in both strata (Appendix Table L-1: Black: slope=0.1495, p<0.001; non-Black: slope=0.0190, p=0.003). The significant interaction was due to the fact that the slope in the Black stratum was steeper than the slope in the non-Black stratum. The adjusted means in the Black stratum increased from 5.138 thousand/mm^3 to 6.476 thousand/mm^3 and to 8.230 thousand/mm^3 over the low, medium, and high initial dioxin levels, whereas the adjusted means in the non-Black stratum only increased from 6.615 thousand/mm^3 to 6.886 thousand/mm^3 and to 7.045 thousand/mm^3.

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

The interaction between current dioxin and time since tour was not significant in the unadjusted analysis of the minimal cohort for WBC count (Table 13-5 [e]: p=0.479). However, there was a marginally significant positive association between WBC count and current dioxin for those Ranch Hands whose time since tour exceeded 18.6 years (p=0.090). The mean WBC counts in this time stratum increased over the current dioxin levels (low: 6.913 thousand/mm^3; medium: 6.961 thousand/mm^3; high: 7.244 thousand/mm^3).

Under the maximal assumption the current dioxin-by-time since tour interaction was not significant (Table 13-5 [f]: p=0.712). There was, however, a marginally significant positive association between WBC count and current dioxin when time since tour was less than or equal to 18.6 years (p=0.059). The means were 6.355, 6.874, and 6.897 thousand/mm^3 for the low, medium, and high initial dioxin levels. There was also a significant positive association when time was greater than 18.6 years (p=0.007). The mean WBC counts in this time stratum were 6.549, 6.826, and 7.311 thousand/mm^3.

When the model for the minimal cohort was adjusted for significant covariates, there was a significant interaction among current dioxin, time, and age (Table 13-5 [g]: p=0.021).

TABLE 13-5.

Analysis of White Blood Cell Count (thousand/mm^3) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean[a]	Slope (Std. Error)[b]	p-Value
a) Minimal	Low	130	6.589	0.0182 (0.0100)	0.071
(n=520)	Medium	259	7.118		
(R^2=0.006)	High	131	6.978		
b) Maximal	Low	185	6.496	0.0260 (0.0074)	<0.001
(n=741)	Medium	370	6.854		
(R^2=0.016)	High	186	7.055		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)	p-Value	Covariate Remarks
c) Minimal	Low	130	****	****	****	INIT*RACE (p<0.001)
(n=520)	Medium	259	****			RACE*PACKYR (p=0.008)
(R^2=0.306)	High	131	****			CSMOK*PACKYR (p<0.001)
d) Maximal	Low	185	****	****	****	INIT*RACE (p=0.001)
(n=741)	Medium	370	****			RACE*PACKYR (p=0.009)
(R^2=0.309)	High	186	****			CSMOK*PACKYR (p<0.001)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm white blood cell count versus log_2 dioxin.

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

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

TABLE 13-5. (Continued)

Analysis of White Blood Cell Count (thousand/mm^3) (Continuous)

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

Assumption	Time (Yrs.)	Mean[a]/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[b]	p-Value
e) Minimal						0.479[c]
(n=520)	≤18.6	6.428	7.173	6.735	0.0077 (0.0163)	0.636[d]
(R^2=0.008)		(72)	(128)	(54)		
	>18.6	6.913	6.961	7.244	0.0227 (0.0134)	0.090[d]
		(58)	(131)	(77)		
f) Maximal						0.712[c]
(n=741)	≤18.6	6.355	6.874	6.897	0.0219 (0.0115)	0.059[d]
(R^2=0.017)		(106)	(191)	(83)		
	>18.6	6.549	6.826	7.311	0.0275 (0.0102)	0.007[d]
		(79)	(178)	(104)		

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

Assumption	Time (Yrs.)	Adj. Mean[a]/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[b]	p-Value	Covariate Remarks
g) Minimal						0.193**[c]	CURR*TIME*AGE
(n=520)	≤18.6	6.520	7.061	6.657	-0.0013 (0.0144)**	0.929**[d]	(p=0.021)
(R^2=0.300)		(72)	(128)	(54)			RACE*PACKYR
	>18.6	6.892	6.850	7.260	0.0222 (0.0117)**	0.059**[d]	(p=0.004)
		(58)	(131)	(77)			CSMOK*PACKYR
							(p<0.001)
h) Maximal						0.197**[c]	CURR*TIME*RACE
(n=741)	≤18.6	6.333	6.758	6.665	0.0135 (0.0098)**	0.169**[d]	(p=0.050)
(R^2=0.312)		(106)	(191)	(83)			RACE*PACKYR
	>18.6	6.314	6.624	7.180	0.0303 (0.0087)**	<0.001**[d]	(p=0.012)
		(79)	(178)	(104)			CSMOK*PACKYR
							(p<0.001)

[a]Transformed from natural logarithm scale.

[b]Slope and standard error based on natural logarithm white blood cell count versus log_2 dioxin.

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

[d]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.

TABLE 13-5. (Continued)

Analysis of White Blood Cell Count (thousand/mm^3) (Continuous)

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

Current Dioxin Category	n	Mean[a]	Contrast	Difference of Means (95% C.I.)[e]	p-Value[f]
Background	783	6.668	All Categories		0.017
Unknown	345	6.700	Unknown vs. Background	0.032 --	0.799
Low	195	6.950	Low vs. Background	0.282 --	0.072
High	187	7.124	High vs. Background	0.456 --	0.005
Total	1,510		(R^2=0.007)		

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

Current Dioxin Category	n	Adj. Mean[a]	Contrast	Difference of Adj. Means (95% C.I.)[e]	p-Value[f]	Covariate Remarks
Background	783	6.591	All Categories		0.010	AGE*CSMOK (p=0.048) AGE*PACKYR (p=0.006)
Unknown	345	6.536	Unknown vs. Background	-0.055 --	0.590	RACE*PACKYR
Low	195	6.771	Low vs. Background	0.180 --	0.159	(p=0.022)
High	187	6.983	High vs. Background	0.392 --	0.004	CSMOK*PACKYR (p<0.001)
Total	1,510		(R^2=0.312)			

[a]Transformed from natural logarithm scale.

[e]Difference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

[f]P-value is based on difference of means on natural logarithm scale.

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.

Age was then divided into two strata, one containing Ranch Hands born in or after 1942, the other containing Ranch Hands born before 1942. In the stratum containing the younger Ranch Hands, the current dioxin-by-time interaction was significant (Appendix Table L-1: p=0.025). There was a nonsignificant negative association between WBC count and current dioxin for time less than or equal to 18.6 years (p=0.662) and a significant positive association for time greater than 18.6 years (p=0.006). The adjusted means in the early tour stratum (time>18.6 years) were 6.846, 6.771, and 7.543 thousand/mm^3 for the low, medium, and high levels of current dioxin.

In the stratum containing the older Ranch Hands, the current dioxin-by-time interaction was not significant (p=0.528). However, in contrast to the pattern found in the younger age stratum, the association between current dioxin and WBC count was greater in the later tour stratum (time ≤18.6 years) than it was in the earlier tour stratum (time>18.6 years). After the current dioxin-by-time-by-age interaction was removed from the model, the current dioxin-by-time interaction remained nonsignificant (p=0.193). The positive association between WBC count and current dioxin for time greater than 18.6 years remained marginally significant (p=0.059).

When the model for the maximal cohort was adjusted for significant covariates, there was a significant interaction between current dioxin, time, and race (Table 13-5 [h]: p=0.050). To study this interaction race was divided into two strata: Black and non-Black. Within the Black stratum, the current dioxin-by-time since tour interaction was marginally significant (Appendix Table L-1: p=0.080). For time less than or equal to 18.6 years, there was a significant positive association between WBC count and current dioxin (p=0.004). The adjusted means were 5.150, 6.180, and 8.070 thousand/mm^3 for the low, medium, and high current dioxin levels. For time greater than 18.6 years, the association was not significant (p=0.333).

Within the non-Black stratum, the current dioxin-by-time since tour interaction was not significant (p=0.117). In contrast to the Black stratum, the association was not significant for time less than or equal to 18.6 years (p=0.356), and was significant for time greater than 18.6 years (p<0.001). For time greater than 18.6 years, the adjusted means were 6.442, 6.819, and 7.333 thousand/mm^3 for the low, medium, and high levels of current dioxin.

After the interaction was removed from the model, the remaining covariates in the adjusted model were the interaction between race and lifetime cigarette smoking history and the interaction between current cigarette smoking and lifetime cigarette smoking history. The current dioxin-by-time since tour interaction remained nonsignificant in this adjusted model (p=0.197). The positive association between WBC count and current dioxin remained significant for time greater than 18.6 years (p<0.001), but became nonsignificant for time less than or equal to 18.6 years (p=0.169).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analysis showed a significant difference in WBC count among the four current dioxin categories (Table 13-5 [i]: p=0.017). The means for the background, unknown, low, and high categories were 6.668, 6.700, 6.950, and 7.124 thousand/mm^3. The mean WBC count for the unknown category was not significantly different from the mean for

the background category (p=0.799), the mean for the low category was marginally higher than the mean for the background category (p=0.072), and the mean for the high category was significantly higher than the mean for the background category (p=0.005).

After the model was adjusted for covariates, the overall contrast remained significant (Table 13-5 [j]: p=0.010). The adjusted WBC count means were 6.591, 6.536, 6.771, and 6.983 thousand/mm^3 for the background, unknown, low, and high categories. The difference between the unknown and background categories remained nonsignificant (p=0.590) and the mean for the high category remained significantly greater than the mean for the background category (p=0.004). However, the difference between the low and background categories became nonsignificant (p=0.159). The covariates that were retained in the model were age-by-current cigarette smoking, age-by-lifetime cigarette smoking history, race-by-lifetime cigarette smoking history, and current cigarette smoking-by-lifetime cigarette smoking history.

White Blood Cell Count (Discrete)

Model 1: Ranch Hands - Initial Dioxin (Categorized)

The overall unadjusted contrast showed no significant association between the level of initial dioxin and the WBC count classification in both the minimal and maximal cohorts (Table 13-6 [a] and [b]: p=0.424 and p=0.328).

After the model was adjusted for covariates, the overall contrast remained nonsignificant in both cohorts (Table 13-6 [c] and [d]: p=0.467 for the minimal, p=0.295 for the maximal).

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

In the unadjusted analysis of the minimal cohort the current dioxin-by-time since tour interaction was not significant for the WBC count classification (Table 13-6 [e]: p=0.179). The overall contrast exhibited no significant association between the level of current dioxin and the WBC count classification within either time stratum (p=0.330 for time≤18.6, p=0.166 for time>18.6). However, when time was restricted to more than 18.6 years, the risk of an abnormally high WBC count was marginally less than 1 for the high versus low contrast (Est. RR=0.13, 95% C.I.: [0.02,1.17], p=0.069). The percentages of abnormally high WBC counts were 8.6, 5.3, and 1.3 percent for the low, medium, and high current dioxin categories within this time stratum.

In the unadjusted analysis of the maximal cohort the current dioxin-by-time since tour interaction was not significant for WBC count (Table 13-6 [f]: p=0.712). The overall contrast was also nonsignificant within both time strata (p=0.631 for time≤18.6, p=0.320 for time>18.6).

After the model for the minimal cohort was adjusted for covariates, the current dioxin-by-time since tour interaction remained nonsignificant (Table 13-6 [g]: p=0.184) as did the overall contrasts (p=0.538 for time≤18.6, p=0.172 for time>18.6). The risk of an abnormally high WBC count for the high versus low contrast remained marginally less than 1 for time greater than 18.6 years (Adj. RR=0.20, 95% C.I.: [0.03,1.18], p=0.076). After the model for

TABLE 13-6.

Analysis of White Blood Cell Count (Discrete)

Ranch Hands - Initial Dioxin (Categorized) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abn. Low	Percent Normal	Percent Abn. High	Initial Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
a) Minimal	Low	130	5.4	90.0	4.6	Overall†		0.424
(n=520)	Medium	259	3.9	90.7	5.4	M vs. L[a]	0.71 (0.26,1.92)	0.500
	High	131	5.3	93.1	1.5	H vs. L[a]	0.96 (0.33,2.81)	0.938
						M vs. L[b]	1.16 (0.44,3.10)	0.766
						H vs. L[b]	0.32 (0.06,1.61)	0.167
b) Maximal	Low	349	6.0	89.7	4.3	Overall†		0.328
(n=741)	Medium	261	3.8	90.8	5.4	M vs. L[a]	0.63 (0.29,1.36)	0.239
	High	131	5.3	93.1	1.5	H vs. L[a]	0.85 (0.35,2.06)	0.727
						M vs. L[b]	1.23 (0.58,2.60)	0.584
						H vs. L[b]	0.34 (0.08,1.52)	0.158

Ranch Hands - Initial Dioxin (Categorized) - Adjusted

Assumption	Initial Dioxin Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) Minimal	Overall†		0.467	AGE (p=0.057)
(n=520)	M vs. L[a]	0.76 (0.28,2.04)	0.588	RACE (p=0.002)
	H vs. L[a]	0.97 (0.33,2.89)	0.957	CSMOK (p<0.001)
	M vs. L[b]	0.70 (0.26,1.94)	0.497	
	H vs. L[b]	0.29 (0.06,1.28)	0.101	
d) Maximal	Overall†		0.295	RACE (p<0.001)
(n=741)	M vs. L[a]	0.64 (0.29,1.40)	0.264	CSMOK (p<0.001)
	H vs. L[a]	0.97 (0.40,2.33)	0.941	
	M vs. L[b]	0.87 (0.40,1.88)	0.725	
	H vs. L[b]	0.31 (0.08,1.26)	0.101	

[a]Abnormal low contrasted with normal.

[b]Abnormal high contrasted with normal.

†Overall test of independence of initial dioxin and white blood cell count.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
M vs. L: Medium initial dioxin category versus low initial dioxin category.
H vs. L: High initial dioxin category versus low initial dioxin category.

TABLE 13-6. (Continued)

Analysis of White Blood Cell Count (Discrete)

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

Assumption	Time	White Blood Cell Category	Percent/(n) Current Dioxin Low	Medium	High	Current Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
e) Minimal (n=520)						C-by-T*		0.179
	≤18.6	Abn. Low	4.2	4.7	9.3	Overall†		0.330
		Normal	94.4	89.8	88.9	M vs. L[a]	1.18 (0.29,4.89)	0.816[c]
		Abn. High	1.4	5.5	1.9	H vs. L[a]	2.37 (0.54,10.36)	0.253[c]
			(72)	(128)	(54)	M vs. L[b]	4.13 (0.50,34.27)	0.189[c]
						H vs. L[b]	1.42 (0.09,23.29)	0.806[c]
	>18.6	Abn. Low	6.9	3.1	2.6	Overall†		0.166
		Normal	84.5	91.6	96.1	M vs. L[a]	0.41 (0.10,1.70)	0.218[c]
		Abn. High	8.6	5.3	1.3	H vs. L[a]	0.33 (0.06,1.88)	0.212[c]
			(58)	(131)	(77)	M vs. L[b]	0.57 (0.17,1.89)	0.360[c]
						H vs. L[b]	0.13 (0.02,1.17)	0.069[c]
f) Maximal (n=741)						C-by-T*		0.712
	≤18.6	Abn. Low	6.1	4.7	9.3	Overall†		0.631
		Normal	89.9	89.8	88.9	M vs. L[a]	0.77 (0.28,2.12)	0.619[c]
		Abn. High	4.0	5.5	1.9	H vs. L[a]	1.55 (0.52,4.60)	0.433[c]
			(198)	(128)	(54)	M vs. L[b]	1.36 (0.48,3.84)	0.567[c]
						H vs. L[b]	0.47 (0.06,3.82)	0.477[c]
	>18.6	Abn. Low	5.9	3.1	2.6	Overall†		0.320
		Normal	89.5	91.6	96.1	M vs. L[a]	0.51 (0.15,1.69)	0.269[c]
		Abn. High	4.6	5.3	1.3	H vs. L[a]	0.41 (0.09,1.95)	0.264[c]
			(153)	(131)	(77)	M vs. L[b]	1.14 (0.39,3.35)	0.810[c]
						H vs. L[b]	0.26 (0.03,2.19)	0.218[c]

[a]Abnormal low contrasted with normal.
[b]Abnormal high contrasted with normal.
[c]Test of significance for relative risk equal to 1 (current dioxin and time categorized).
*Test of significance of current dioxin-by-time interaction.
†Overall test of independence of current dioxin and white blood cell count within time stratum.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
M vs. L: Medium current dioxin category versus low current dioxin category.
H vs. L: High current dioxin category versus low current dioxin category.

TABLE 13-6. (Continued)

Analysis of White Blood Cell Count (Discrete)

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

Assumption	Time (Yrs.)	Current Dioxin Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
g) Minimal		C-by-T*		0.184	AGE (p=0.099)
(n=520)	≤18.6	Overall†		0.538	RACE (p<0.001)
		M vs. L[a]	1.16 (0.30,4.47)	0.830[c]	CSMOK (p<0.001)
		H vs. L[a]	2.36 (0.56,9.95)	0.241[c]	
		M vs. L[b]	2.04 (0.36,11.60)	0.421[c]	
		H vs. L[b]	1.15 (0.13,10.48)	0.900[c]	
	>18.6	Overall†		0.172	
		M vs. L[a]	0.36 (0.09,1.43)	0.147[c]	
		H vs. L[a]	0.31 (0.06,1.54)	0.151[c]	
		M vs. L[b]	0.41 (0.12,1.36)	0.145[c]	
		H vs. L[b]	0.20 (0.03,1.18)	0.076[c]	
h) Maximal		C-by-T*		0.529	RACE (p<0.001)
(n=741)	≤18.6	Overall†		0.676	CSMOK (p<0.001)
		M vs. L[a]	0.84 (0.31,2.31)	0.737[c]	
		H vs. L[a]	2.09 (0.70,6.20)	0.184[c]	
		M vs. L[b]	0.97 (0.34,2.77)	0.954[c]	
		H vs. L[b]	0.43 (0.07,2.75)	0.375[c]	
	>18.6	Overall†		0.427	
		M vs. L[a]	0.46 (0.14,1.52)	0.201[c]	
		H vs. L[a]	0.42 (0.10,1.85)	0.251[c]	
		M vs. L[b]	0.92 (0.31,2.71)	0.880[c]	
		H vs. L[b]	0.34 (0.05,2.19)	0.259[c]	

[a]Abnormal low contrasted with normal.

[b]Abnormal high contrasted with normal.

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

*Overall test of significance of current dioxin-by-time interaction.

†Overall test of independence of current dioxin and white blood cell count within time stratum.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
M vs. L: Medium current dioxin category versus low current dioxin category.
H vs. L: High current dioxin category versus low current dioxin category.

TABLE 13-6. (Continued)

Analysis of White Blood Cell Count (Discrete)

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

Current Dioxin Category	n	Percent Abn. Low	Percent Normal	Percent Abn. High	Contrast	Abnormal Low versus Normal: Est. Relative Risk (95% C.I.)	Abnormal Low versus Normal: p-Value	Abnormal High versus Normal: Est. Relative Risk (95% C.I.)	Abnormal High versus Normal: p-Value
Background	783	7.8	86.3	5.9					
Unknown	345	6.7	87.8	5.5	Unknown vs. Background	0.84 (0.51,1.38)	0.496	0.92 (0.53,1.60)	0.771
Low	195	4.1	91.3	4.6	Low vs. Background	0.50 (0.23,1.06)	0.071	0.74 (0.36,1.55)	0.429
High	187	4.8	92.0	3.2	High vs. Background	0.58 (0.28,1.19)	0.137	0.51 (0.22,1.22)	0.132
Total	1,510						All categories: p=0.285		

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

Current Dioxin Category	n	Contrast	Abnormal Low versus Normal: Adj. Relative Risk (95% C.I.)	Abnormal Low versus Normal: p-Value	Abnormal High versus Normal: Adj. Relative Risk (95% C.I.)	Abnormal High versus Normal: p-Value	Covariate Remarks
Background	783						RACE (p<0.001) CSMOK (p<0.001)
Unknown	345	Unknown vs. Background	0.93 (0.56,1.54)	0.780	0.84 (0.48,1.50)	0.577	
Low	195	Low vs. Background	0.58 (0.27,1.22)	0.151	0.62 (0.29,1.30)	0.206	
High	187	High vs. Background	0.63 (0.31,1.30)	0.214	0.44 (0.19,1.05)	0.063	
Total	1,510			All categories: p=0.215			

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

the maximal cohort was adjusted, the current dioxin-by-time since tour interaction also remained nonsignificant (Table 13-6 [h]: p=0.529) as did the overall contrasts (p=0.676 for time≤18.6, p=0.427 for time>18.6).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast in the unadjusted model showed no significant association between the four current dioxin categories and the WBC count classifications (Table 13-6 [i]: p=0.285). However, the risk of an abnormally low WBC count was marginally less than 1 for the low versus background contrast (Est. RR=0.50, 95% C.I.: [0.23,1.06], p=0.071). In the background, unknown, low, and high current dioxin categories, 7.8, 6.7, 4.1, and 4.8 percent of the participants had an abnormally low WBC count.

After adjusting the model for race and current cigarette smoking, the overall contrast remained nonsignificant (Table 13-6 [j]: p=0.215). However, the risk of an abnormally low WBC count for the low versus background contrast became nonsignificant (p=0.151), and the risk of an abnormally high WBC count for the high versus background contrast became marginally significant (Adj. RR=0.44, 95% C.I.: [0.19,1.05], p=0.063). The percentages of abnormally high WBC counts for the background, unknown, low, and high categories were 5.9, 5.5, 4.6, and 3.2 percent.

Hemoglobin (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analysis of the minimal cohort showed no significant association between hemoglobin and initial dioxin (Table 13-7 [a]: p=0.232). A marginally significant association was exhibited, though, for the maximal cohort (Table 13-7 [b]: p=0.079). The means for the low, medium, and high levels of initial dioxin were 15.619, 15.719, and 15.790 gm/dl.

When the minimal analysis was adjusted for covariates, the association between hemoglobin and initial dioxin remained nonsignificant (Table 13-7 [c]: p=0.316). The association became nonsignificant in the maximal analysis after the model was adjusted for race and current cigarette smoking (Table 13-7 [d]: p=0.120).

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

The current dioxin-by-time since tour interaction was not significant for the minimal cohort in the unadjusted analysis of hemoglobin (Table 13-7 [e]: p=0.875). For the maximal cohort, the current dioxin-by-time since tour interaction was significant (Table 13-7 [f]: p=0.036). Within the maximal cohort, the association between hemoglobin and current dioxin was significantly positive when time was less than or equal to 18.6 years (p=0.010), and was negative, although nonsignificant, when time was greater than 18.6 years (p=0.795). The means were 15.518, 15.681, and 15.863 gm/dl for the low, medium, and high levels of current dioxin in the later tour stratum (time≤18.6 years) and were 15.938, 15.673, and 15.742 gm/dl in the earlier tour stratum (time>18.6 years).

The interaction between current dioxin and time since tour remained nonsignificant in the adjusted analysis of the minimal cohort (Table 13-7 [g]: p=0.969). For the maximal

TABLE 13-7.

Analysis of Hemoglobin (gm/dl) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal (n=520) (R^2=0.003)	Low	130	15.641	0.0473 (0.0395)	0.232
	Medium	259	15.768		
	High	131	15.768		
b) Maximal (n=741) (R^2=0.004)	Low	185	15.619	0.0500 (0.0284)	0.079
	Medium	370	15.719		
	High	186	15.790		

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=520) (R^2=0.062)	Low	130	15.525	0.0387 (0.0386)	0.316	RACE (p=0.103) CSMOK (p<0.001)
	Medium	259	15.616			
	High	131	15.624			
d) Maximal (n=741) (R^2=0.078)	Low	185	15.500	0.0426 (0.0274)	0.120	RACE (p=0.107) CSMOK (p<0.001)
	Medium	370	15.588			
	High	186	15.657			

[a]Slope and standard error based on hemoglobin versus log_2 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 13-7. (Continued)

Analysis of Hemoglobin (gm/dl) (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						0.875[b]
(n=520)	≤18.6	15.701	15.784	15.865	0.0692 (0.0644)	0.283[c]
(R^2=0.006)		(72)	(128)	(54)		
	>18.6	15.598	15.744	15.690	0.0561 (0.0527)	0.287[c]
		(58)	(131)	(77)		
f) Maximal						0.036[b]
(n=741)	≤18.6	15.518	15.681	15.863	0.1135 (0.0440)	0.010[c]
(R^2=0.010)		(106)	(191)	(83)		
	>18.6	15.938	15.673	15.742	-0.0101 (0.0389)	0.795[c]
		(79)	(178)	(104)		

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						0.969[b]	RACE (p=0.115)
(n=520)	≤18.6	15.595	15.629	15.713	0.0522 (0.0628)	0.406[c]	CSMOK (p<0.001)
(R^2=0.065)		(72)	(128)	(54)			
	>18.6	15.450	15.598	15.566	0.0554 (0.0512)	0.280[c]	
		(58)	(131)	(77)			
h) Maximal						0.073[b]	RACE (p=0.112)
(n=741)	≤18.6	15.439	15.573	15.722	0.0964 (0.0425)	0.024[c]	CSMOK (p<0.001)
(R^2=0.083)		(106)	(191)	(83)			
	>18.6	15.795	15.553	15.633	-0.0056 (0.0375)	0.881[c]	
		(79)	(178)	(104)			

[a]Slope and standard error based on hemoglobin versus log_2 dioxin.

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

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

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

TABLE 13-7. (Continued)

Analysis of Hemoglobin (gm/dl) (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	783	15.652	All Categories		0.323
Unknown	345	15.673	Unknown vs. Background	0.021 (-0.111,0.153)	0.755
Low	195	15.740	Low vs. Background	0.088 (-0.075,0.252)	0.291
High	187	15.796	High vs. Background	0.144 (-0.022,0.310)	0.090
Total	1,510		(R^2=0.002)		

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	783	15.467	All Categories		0.643	AGE (p=0.031)
Unknown	345	15.451	Unknown vs. Background	-0.016 (-0.142,0.110)	0.808	RACE (p<0.001)
Low	195	15.525	Low vs. Background	0.058 (-0.098,0.214)	0.464	CSMOK (p<0.001)
High	187	15.548	High vs. Background	0.081 (-0.079,0.242)	0.320	
Total	1,510		(R^2=0.100)			

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.

cohort this interaction became marginally significant (Table 13-7 [h]: p=0.073). However, the association between hemoglobin and current dioxin remained positive and significant for time less than or equal to 18.6 years (p=0.024) and remained negative and nonsignificant for time greater than 18.6 years (p=0.881). The covariates that were retained in this model were race and current cigarette smoking.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

No significant association with hemoglobin was exhibited by the overall contrast of the four current dioxin categories in the unadjusted analysis (Table 13-7 [i]: p=0.323). However, the mean for the high category was marginally higher than the mean for the background category (p=0.090). The hemoglobin means for the background, unknown, low, and high categories were 15.652, 15.673, 15.740, and 15.796 gm/dl.

After adjusting the model for significant covariates, the overall contrast remained nonsignificant (Table 13-7 [j]: p=0.643) and the difference between the high and background categories became nonsignificant for the analysis of hemoglobin (p=0.320). The significant covariates in this model were age, race, and current cigarette smoking.

Hemoglobin (Discrete)

Model 1: Ranch Hands - Initial Dioxin (Categorized)

There was no significant association exhibited between the initial dioxin categories (low, medium, and high) and the hemoglobin classifications (low, normal, high) for either the minimal or maximal cohort in the unadjusted and the adjusted analyses (Table 13-8 [a-d]: p>0.65 for all overall contrasts).

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

The interaction between current dioxin and time since tour for the minimal cohort was not significant for the unadjusted analysis of the hemoglobin concentrations (Table 13-8 [e]: p=0.136). For the maximal cohort, the current dioxin-by-time since tour interaction was significant (Table 13-8 [f]: p=0.006). When time since tour was less than or equal to 18.6 years, the overall contrast showed a significant association between the current dioxin categories and the hemoglobin classifications (p=0.012). When time was greater than 18.6 years, the association was not significant (p=0.553). However, the risk of an abnormally low hemoglobin concentration, in this time stratum, was marginally significant for the medium versus low current dioxin contrast (Est. RR=2.72, 95% C.I.: [0.83,8.94], p=0.100). The percentages of Ranch Hands, in the maximal cohort, with abnormally low hemoglobin in the low, medium, and high current dioxin categories were 2.6, 6.9, and 5.2 percent for time over 18.6 years.

The current dioxin-by-time since tour interaction remained nonsignificant in the adjusted analysis of the minimal cohort (Table 13-8 [g]: p=0.334). In the adjusted analysis of the maximal cohort, the current dioxin-by-time since tour interaction remained significant (Table 13-8 [h]: p=0.043), but the overall contrast for time less than or equal to 18.6 years became nonsignificant (p=0.116). For time greater than 18.6 years, the risk of an abnormally low hemoglobin concentration, for the medium versus low contrast, remained marginally significant (p=0.076). Race and the interaction between current cigarette smoking and

TABLE 13-8.

Analysis of Hemoglobin (Discrete)

Ranch Hands - Initial Dioxin (Categorized) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abn. Low	Percent Normal	Percent Abn. High	Initial Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
a) Minimal (n=520)	Low	130	3.9	96.2	0.0	Overall†		0.703
	Medium	259	3.9	94.6	1.5	M vs. L[a]	1.01 (0.34,3.00)	0.983
	High	131	3.1	96.2	0.8	H vs. L[a]	0.80 (0.21,3.00)	0.739
						M vs. L[b]	--	--
						H vs. L[b]	--	--
b) Maximal (n=741)	Low	349	4.0	95.4	0.6	Overall†		0.778
	Medium	261	3.8	94.6	1.5	M vs. L[a]	0.96 (0.42,2.20)	0.928
	High	131	3.1	96.2	0.8	H vs. L[a]	0.76 (0.24,2.34)	0.627
						M vs. L[b]	2.70 (0.49,14.83)	0.254
						H vs. L[b]	1.32 (0.12,14.73)	0.820

Ranch Hands - Initial Dioxin (Categorized) - Adjusted

Assumption	Initial Dioxin Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
c) Minimal (n=520)	Overall†		0.694	CSMOK (p<0.001)
	M vs. L[a]	1.02 (0.35,3.02)	0.968	
	H vs. L[a]	0.80 (0.22,2.98)	0.743	
	M vs. L[b]	--	--	
	H vs. L[b]	--	--	
d) Maximal (n=741)	Overall†		0.896	AGE (p=0.076)
	M vs. L[a]	0.99 (0.44,2.22)	0.983	RACE (p=0.100)
	H vs. L[a]	0.93 (0.32,2.74)	0.900	CSMOK (p<0.001)
	M vs. L[b]	2.09 (0.46,9.47)	0.341	
	H vs. L[b]	2.04 (0.29,14.15)	0.472	

[a]Abnormal low contrasted with normal.

[b]Abnormal high contrasted with normal.

†Overall test of independence of initial dioxin and hemoglobin.

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.

Notes: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
M vs. L: Medium initial dioxin category versus low initial dioxin category.
H vs. L: High initial dioxin category versus low initial dioxin category.

TABLE 13-8. (Continued)

Analysis of Hemoglobin (Discrete)

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

Assumption	Time (Yrs.)	Hemoglobin Category	Percent/(n) Current Dioxin Low	Medium	High	Current Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
e) Minimal						C-by-T*		0.136
(n=520)	≤18.6	Abn. Low	4.2	0.0	1.9	Overall†		0.116
		Normal	95.8	98.4	98.2	M vs. L[a]	--	--
		Abn. High	0.0	1.6	0.0	H vs. L[a]	0.46 (0.05,4.19)	0.493[c]
			(72)	(128)	(54)	M vs. L[b]	--	--
						H vs. L[b]	--	--
	>18.6	Abn. Low	3.5	6.9	5.2	Overall†		0.743
		Normal	96.6	91.6	93.5	M vs. L[a]	2.02 (0.44,9.38)	0.367[c]
		Abn. High	0.0	1.5	1.3	H vs. L[a]	1.52 (0.28,8.29)	0.630[c]
			(58)	(131)	(77)	M vs. L[b]	--	--
						H vs. L[b]	--	--
f) Maximal						C-by-T*		0.006
(n=741)	≤18.6	Abn. Low	5.1	0.0	1.9	Overall†		0.012
		Normal	95.0	98.4	98.2	M vs. L[a]	--	--
		Abn. High	0.0	1.6	0.0	H vs. L[a]	0.39 (0.05,2.83)	0.349[c]
			(198)	(128)	(54)	M vs. L[b]	--	--
						H vs. L[b]	--	--
	>18.6	Abn. Low	2.6	6.9	5.2	Overall†		0.553
		Normal	96.1	91.6	93.5	M vs. L[a]	2.72 (0.83,8.94)	0.100[c]
		Abn. High	1.3	1.5	1.3	H vs. L[a]	2.05 (0.51,8.27)	0.315[c]
			(153)	(131)	(77)	M vs. L[b]	1.23 (0.18,8.41)	0.836[c]
						H vs. L[b]	1.07 (0.11,10.94)	0.953[c]

[a]Abnormal low contrasted with normal.

[b]Abnormal high contrasted with normal.

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

*Test of significance of current dioxin-by-time interaction.

†Overall test of independence of current dioxin and hemoglobin within time stratum.

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.

Note: Minimal- -Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal- -Low: >5-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
M vs. L: Medium current dioxin category versus low current dioxin category.
H vs. L: High current dioxin category versus low current dioxin category.

TABLE 13-8. (Continued)

Analysis of Hemoglobin (Discrete)

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

Assumption	Time (Yrs.)	Current Dioxin Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
g) Minimal (n=520)		C-by-T*		0.334	RACE (p=0.006)
	≤18.6	Overall†		0.446	CSMOK*PACKYR (p=0.007)
		M vs. L[a]	--	--	
		H vs. L[a]	0.91 (0.16,5.20)	0.912[c]	
		M vs. L[b]	--	--	
		H vs. L[b]	--	--	
	>18.6	Overall†		0.748	
		M vs. L[a]	2.21 (0.53,9.17)	0.274[c]	
		H vs. L[a]	1.93 (0.41,9.14)	0.410[c]	
		M vs. L[b]	--	--	
		H vs. L[b]	--	--	
h) Maximal (n=741)		C-by-T*		0.043	RACE (p=0.015)
	≤18.6	Overall†		0.116	CSMOK*PACKYR (p=0.010)
		M vs. L[a]	--	--	
		H vs. L[a]	0.72 (0.16,3.35)	0.679[c]	
		M vs. L[b]	--	--	
		H vs. L[b]	--	--	
	>18.6	Overall†		0.411	
		M vs. L[a]	2.79 (0.90,8.69)	0.076[c]	
		H vs. L[a]	2.23 (0.61,8.14)	0.226[c]	
		M vs. L[b]	1.14 (0.22,5.79)	0.877[c]	
		H vs. L[b]	1.79 (0.30,10.78)	0.524[c]	

[a]Abnormal low contrasted with normal.
[b]Abnormal high contrasted with normal.
[c]Test of significance for relative risk equal to 1 (current dioxin and time categorized).
*Test of significance of current dioxin-by-time interaction.
†Overall test of independence of current dioxin and hemoglobin within time stratum.
--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Notes: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
M vs. L: Medium current dioxin category versus low current dioxin category.
H vs. L: High current dioxin category versus low current dioxin category.

TABLE 13-8. (Continued)

Analysis of Hemoglobin (Discrete)

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

Current Dioxin Category	n	Percent Abn. Low	Percent Normal	Percent Abn. High	Contrast	Abnormal Low versus Normal: Est. Relative Risk (95% C.I.)	Abnormal Low versus Normal: p-Value	Abnormal High versus Normal: Est. Relative Risk (95% C.I.)	Abnormal High versus Normal: p-Value
Background	783	4.3	94.5	1.2					
Unknown	345	3.5	95.9	0.6	Unknown vs. Background	0.79 (0.40,1.55)	0.491	0.50 (0.11,2.31)	0.372
Low	195	4.6	93.3	2.1	Low vs. Background	1.08 (0.51,2.28)	0.849	1.80 (0.55,5.92)	0.331
High	187	2.7	96.8	0.5	High vs. Background	0.60 (0.23,1.56)	0.294	0.45 (0.06,3.61)	0.455
Total	1,510						All categories: p=0.576		

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

Current Dioxin Category	n	Contrast	Abnormal Low versus Normal: Adj. Relative Risk (95% C.I.)	Abnormal Low versus Normal: p-Value	Abnormal High versus Normal: Adj. Relative Risk (95% C.I.)	Abnormal High versus Normal: p-Value	Covariate Remarks
Background	783						RACE (p=0.001) CSMOK (p<0.001)
Unknown	345	Unknown vs. Background	0.88 (0.45,1.72)	0.716	0.54 (0.13,2.24)	0.393	
Low	195	Low vs. Background	1.11 (0.52,2.35)	0.785	1.81 (0.57,5.74)	0.315	
High	187	High vs. Background	0.67 (0.27,1.70)	0.402	0.57 (0.10,3.42)	0.539	
Total	1,510			All categories: p=0.703			

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.

lifetime cigarette smoking history were the significant covariates that were retained in the model.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

There was no significant association exhibited between the hemoglobin classifications and the four current dioxin categories in the unadjusted analysis (Table 13-8 [i]: p=0.576). In the adjusted analysis, the association was also nonsignificant (Table 13-8 [j]: p=0.703).

Hematocrit (Continuous)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The association between hematocrit and initial dioxin was not significant under the minimal assumption in the unadjusted analysis (Table 13-9 [a]: p=0.299). However, under the maximal assumption, the association was marginally significant (Table 13-9 [b]: p=0.070). The positive association was exemplified by the increasing means (44.982, 45.331, and 45.515 percent) over the low, medium, and high categories of initial dioxin.

The association in the adjusted analysis remained nonsignificant under the minimal assumption (Table 13-9 [c]: p=0.324). Under the maximal assumption, the association became nonsignificant after adjusting for current cigarette smoking (Table 13-9 [d]: p=0.105).

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

The interaction between current dioxin and time since tour was not significant in the unadjusted analysis of hematocrit under the minimal assumption (Table 13-9 [e]: p=0.904). Under the maximal assumption, this interaction was marginally significant (Table 13-9 [f]: p=0.063). For those Ranch Hands in the maximal cohort whose time since tour was less than or equal to 18.6 years, there was a significant positive association between hematocrit and current dioxin (p=0.018). The mean hematocrit levels were 44.697, 45.171, and 45.676 percent for the low, medium, and high levels of current dioxin. For those Ranch Hands whose time since tour was greater than 18.6 years, the association was negative but nonsignificant (p=0.901).

The adjusted analysis of the minimal cohort continued to produce a nonsignificant interaction between current dioxin and time since tour (Table 13-9 [g]: p=0.968). The current dioxin-by-time since tour interaction became nonsignificant for the maximal cohort after the model was adjusted for current cigarette smoking (Table 13-9 [h]: p=0.116). However, the association between hematocrit and current dioxin remained significant and positive for time less than or equal to 18.6 years and remained nonsignificant and negative for time greater than 18.6 years (p=0.037 for time$\leq$18.6; p=0.989 for time>18.6).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast of the four current dioxin categories exhibited no significant association between hematocrit and current dioxin in the unadjusted analysis (Table 13-9 [i]: p=0.428).

TABLE 13-9.

Analysis of Hematocrit (Percent) (Continuous)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)[a]	p-Value
a) Minimal	Low	130	45.113	0.1183 (0.1138)	0.299
(n=520)	Medium	259	45.500		
(R^2=0.002)	High	131	45.398		
b) Maximal	Low	185	44.982	0.1485 (0.0819)	0.070
(n=741)	Medium	370	45.331		
(R^2=0.004)	High	186	45.515		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
c) Minimal	Low	130	45.160	0.1091 (0.1104)	0.324	CSMOK (p<0.001)
(n=520)	Medium	259	45.462			
(R^2=0.063)	High	131	45.427			
d) Maximal	Low	185	45.037	0.1278 (0.0788)	0.105	CSMOK (p<0.001)
(n=741)	Medium	370	45.305			
(R^2=0.081)	High	186	45.512			

[a]Slope and standard error based on hematocrit versus log_2 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 13-9. (Continued)

Analysis of Hematocrit (Percent) (Continuous)

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

Assumption	Time (Yrs.)	Mean/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[a]	p-Value
e) Minimal (n=520) (R^2=0.003)	≤18.6	45.263 (72)	45.477 (128)	45.570 (54)	0.1624 (0.1855)	0.904[b] 0.382[c]
	>18.6	45.126 (58)	45.450 (131)	45.251 (77)	0.1335 (0.1518)	0.380[c]
f) Maximal (n=741) (R^2=0.010)	≤18.6	44.697 (106)	45.171 (191)	45.676 (83)	0.3016 (0.1270)	0.063[b] 0.018[c]
	>18.6	45.877 (79)	45.226 (178)	45.466 (104)	-0.0140 (0.1123)	0.901[c]

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

Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin Low	Medium	High	Adj. Slope (Std. Error)[a]	p-Value	Covariate Remarks
g) Minimal (n=520) (R^2=0.064)	≤18.6	45.331 (72)	45.438 (128)	45.596 (54)	0.1345 (0.1800)	0.968[b] 0.455[c]	CSMOK (p<0.001)
	>18.6	45.093 (58)	45.411 (131)	45.324 (77)	0.1440 (0.1472)	0.329[c]	
h) Maximal (n=741) (R^2=0.084)	≤18.6	44.814 (106)	45.183 (191)	45.617 (83)	0.2554 (0.1223)	0.116[b] 0.037[c]	CSMOK (p<0.001)
	>18.6	45.820 (79)	45.191 (178)	45.477 (104)	-0.0016 (0.1081)	0.989[c]	

[a]Slope and standard error based on hematocrit versus log_2 dioxin.

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

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

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