

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 $\mu\text{g}/\text{kg}$, 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 $\mu\text{g}/\text{kg}$ 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-secreting 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/mm³ versus 249,061/mm³) 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/mm³. 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/mm³), WBC count (thousand/mm³), hemoglobin (gm/dl), hematocrit (percent), MCV (cubic micra), MCH (micromicrogram), MCHC (gm/dl), platelet count (thousand/mm³), 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

Variable (Units)	Dependent Variables			Candidate Covariates	Statistical Analyses
	Data Source	Data Form	Cutpoints		
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 - Log₂ (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)		Categorized Current Dioxin	
		Minimal	Maximal	Ranch Hand	Comparison
Platelet Count	DEP	1	1	0	0
Temperature $\geq 100^\circ\text{F}$ 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/mm³)
(Continuous)

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted						
Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)^a	p-Value	
a) Minimal (n=520) (R ² =0.001)	Low	130	4.935	0.0105 (0.0136)		
	Medium	259	4.990			
	High	131	4.955			
b) Maximal (n=741) (R ² =0.005)	Low	185	4.908	0.0194 (0.0098)		
	Medium	370	4.963			
	High	186	4.976			
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)^a	p-Value	Covariate Remarks
c) Minimal (n=520) (R ² =0.010)	Low	130	4.946	0.0034 (0.0140)		AGE (p=0.035)
	Medium	259	4.992			
	High	131	4.942			
d) Maximal (n=741) (R ² =0.039)	Low	185	5.002	0.0162 (0.0099)		AGE (p=0.052) RACE*CSMOK (p=0.030)
	Medium	370	5.050			
	High	186	5.057			

^aSlope and standard error based on red blood cell count versus log₂ 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/mm³)
(Continuous)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Mean/(n) Current Dioxin			Slope (Std. Error)^a	p-Value
		Low	Medium	High		
e) Minimal (n=520) (R ² =0.006)	≤18.6	4.975 (72)	4.999 (128)	4.983 (54)	0.0110 (0.0222)	0.710 ^b 0.621 ^c
	>18.6	4.897 (58)	4.965 (131)	4.955 (77)		0.0216 (0.0182)
f) Maximal (n=741) (R ² =0.007)	≤18.6	4.891 (106)	4.963 (191)	5.010 (83)	0.0343 (0.0153)	0.208 ^b 0.025 ^c
	>18.6	4.965 (79)	4.929 (178)	4.980 (104)		0.0086 (0.0135)

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin			Adj. Slope (Std. Error)^a	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=520) (R ² =0.012)	≤18.6	4.983 (72)	4.994 (128)	4.960 (54)	0.0013 (0.0228)	0.660 ^b 0.953 ^c	AGE (p=0.078)
	>18.6	4.916 (58)	4.971 (131)	4.949 (77)			
h) Maximal (n=741) (R ² =0.049)	≤18.6	5.015** (106)	5.082** (191)	5.116** (83)	0.0283 (0.0154)**	0.213** ^b 0.067** ^c	CURR*TIME*AGE (p=0.038) CSMOK (p=0.009)
	>18.6	5.102** (79)	5.050** (178)	5.092** (104)			

^aSlope and standard error based on red blood cell count versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest of significance for slope different from 0 (current dioxin continuous, time categorized).

**Log₂ (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); 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: Log₂ (current dioxin).

TIME: Time since tour.

TABLE 13-3. (Continued)
Analysis of Red Blood Cell Count (million/mm³)
(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)
Unknown	345	4.994	Unknown vs. Background	-0.036 (-0.083,0.010)	0.128	RACE (p<0.001)
Low	195	5.025	Low vs. Background	-0.006 (-0.063,0.052)	0.842	CSMOK (p<0.001)
High	187	5.038	High vs. Background	0.007 (-0.052,0.066)	0.816	PACKYR (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/mm³ 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 - Log₂ (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/mm³, 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/mm³. 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/mm³.

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/mm³ 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/mm³.

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 - Log₂ (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 - Log₂ (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 - Log₂ (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 - Log₂ (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)

^aRelative 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 - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal Low/(n)			Est. Relative Risk (95% C.I.)^a	p-Value
		Low	Medium	High		
e) Minimal (n=520)	≤18.6	1.4 (72)	1.6 (128)	0.0 (54)	0.29 (0.04,2.22)	0.066 ^b 0.232 ^c
	>18.6	3.5 (58)	2.3 (131)	6.5 (77)		
f) Maximal (n=741)	≤18.6	3.8 (106)	1.6 (191)	0.0 (83)	0.47 (0.19,1.19)	0.012 ^b 0.110 ^c
	>18.6	1.3 (79)	2.3 (178)	5.8 (104)		

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)^a	p-Value	Covariate Remarks
g) Minimal (n=520)	≤18.6	0.29 (0.04,2.22)	0.066 ^b 0.232 ^c	--
	>18.6	1.32 (0.84,2.06)	0.229 ^c	
h) Maximal (n=741)	≤18.6	0.50 (0.19,1.32)	0.011 ^b 0.159 ^c	AGE (p=0.022)
	>18.6	1.58 (1.08,2.31)	0.018 ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 \leq 10 ppt.
 Unknown (Ranch Hands): Current Dioxin \leq 10 ppt.
 Low (Ranch Hands): 15 ppt < Current Dioxin \leq 33.3 ppt.
 High (Ranch Hands): Current Dioxin >33.3 ppt.

White Blood Cell Count (Continuous)

Model 1: Ranch Hands - Log₂ (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/mm³. 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/mm³ 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/mm³ 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/mm³ to 6.476 thousand/mm³ and to 8.230 thousand/mm³ over the low, medium, and high initial dioxin levels, whereas the adjusted means in the non-Black stratum only increased from 6.615 thousand/mm³ to 6.886 thousand/mm³ and to 7.045 thousand/mm³.

Model 2: Ranch Hands - Log₂ (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/mm³; medium: 6.961 thousand/mm³; high: 7.244 thousand/mm³).

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/mm³ 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/mm³.

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/mm³)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted						
Assumption	Initial Dioxin	n	Mean^a	Slope (Std. Error)^b	p-Value	
a) Minimal (n=520) (R ² =0.006)	Low	130	6.589	0.0182 (0.0100)	0.071	
	Medium	259	7.118			
	High	131	6.978			
b) Maximal (n=741) (R ² =0.016)	Low	185	6.496	0.0260 (0.0074)	<0.001	
	Medium	370	6.854			
	High	186	7.055			

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)	p-Value	Covariate Remarks
c) Minimal (n=520) (R ² =0.306)	Low	130	****	****	****	INIT*RACE (p<0.001) RACE*PACKYR (p=0.008) CSMOK*PACKYR (p<0.001)
	Medium	259	****			
	High	131	****			
d) Maximal (n=741) (R ² =0.309)	Low	185	****	****	****	INIT*RACE (p=0.001) RACE*PACKYR (p=0.009) CSMOK*PACKYR (p<0.001)
	Medium	370	****			
	High	186	****			

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm white blood cell count versus log₂ dioxin.

****Log₂ (initial dioxin)-by-covariate interaction (p≤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: Log₂ (initial dioxin).

TABLE 13-5. (Continued)

Analysis of White Blood Cell Count (thousand/mm³)
(Continuous)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted

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

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted

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

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm white blood cell count versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope equal to 0 (current dioxin continuous, time categorized).

**Log₂ (current dioxin)-by-time-by-covariate interaction (0.01<p≤0.05); 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/mm³)
(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 (p=0.022)
Low	195	6.771	Low vs. Background	0.180 --	0.159	
High	187	6.983	High vs. Background	0.392 --	0.004	CSMOK*PACKYR (p<0.001)
Total	1,510		(R ² =0.312)			

^aTransformed from natural logarithm scale.

^eDifference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

^fP-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/mm³ 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/mm³ 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/mm³ 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/mm³. 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 $\text{time} \leq 18.6$, $p=0.166$ for $\text{time} > 18.6$). 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 $\text{time} \leq 18.6$, $p=0.320$ for $\text{time} > 18.6$).

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 $\text{time} \leq 18.6$, $p=0.172$ for $\text{time} > 18.6$). 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			Initial Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Abn. Low	Normal	Abn. High			
a) Minimal (n=520)	Low	130	5.4	90.0	4.6	Overall [†]		0.424
	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 (n=741)	Low	349	6.0	89.7	4.3	Overall [†]		0.328
	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 (n=520)	Overall [†]		0.467	AGE (p=0.057)
	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 (n=741)	Overall [†]		0.295	RACE (p<0.001)
	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	

^aAbnormal low contrasted with normal.

^bAbnormal 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			Current Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
e) Minimal (n=520)	≤18.6	Abn. Low	4.2	4.7	9.3	C-by-T*		0.179
		Normal	94.4	89.8	88.9	Overall†		0.330
		Abn. High	1.4	5.5	1.9	M vs. L ^a	1.18 (0.29,4.89)	0.816 ^c
			(72)	(128)	(54)	H vs. L ^a	2.37 (0.54,10.36)	0.253 ^c
						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)	≤18.6	Abn. Low	6.1	4.7	9.3	C-by-T*		0.712
		Normal	89.9	89.8	88.9	Overall†		0.631
		Abn. High	4.0	5.5	1.9	M vs. L ^a	0.77 (0.28,2.12)	0.619 ^c
			(198)	(128)	(54)	H vs. L ^a	1.55 (0.52,4.60)	0.433 ^c
						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

^aAbnormal low contrasted with normal.

^bAbnormal high contrasted with normal.

^cTest 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 (n=520)	≤18.6	C-by-T*		0.184	AGE (p=0.099) RACE (p<0.001) CSMOK (p<0.001)
		Overall†		0.538	
		M vs. L ^a	1.16 (0.30,4.47)	0.830 ^c	
		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 (n=741)	≤18.6	C-by-T*		0.529	RACE (p<0.001) CSMOK (p<0.001)
		Overall†		0.676	
		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	

^aAbnormal low contrasted with normal.

^bAbnormal high contrasted with normal.

^cTest 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			Contrast	Abnormal Low versus Normal		Abnormal High versus Normal	
		Abn. Low	Normal	Abn. High		Est. Relative Risk (95% C.I.)	p-Value	Est. Relative Risk (95% C.I.)	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		Abnormal High versus Normal		Covariate Remarks
			Adj. Relative Risk (95% C.I.)	p-Value	Adj. Relative Risk (95% C.I.)	p-Value	
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 $\text{time}\leq 18.6$, $p=0.427$ for $\text{time}>18.6$).

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 - Log₂ (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 - Log₂ (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 ($\text{time}\leq 18.6$ years) and were 15.938, 15.673, and 15.742 gm/dl in the earlier tour stratum ($\text{time}>18.6$ 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 - Log₂ (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 - Log₂ (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			

^aSlope and standard error based on hemoglobin versus log₂ 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 - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Mean/(n) Current Dioxin			Slope (Std. Error) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=520) (R ² =0.006)	≤18.6	15.701 (72)	15.784 (128)	15.865 (54)	0.0692 (0.0644)	0.875 ^b 0.283 ^c
	>18.6	15.598 (58)	15.744 (131)	15.690 (77)		0.0561 (0.0527)
f) Maximal (n=741) (R ² =0.010)	≤18.6	15.518 (106)	15.681 (191)	15.863 (83)	0.1135 (0.0440)	0.036 ^b 0.010 ^c
	>18.6	15.938 (79)	15.673 (178)	15.742 (104)		-0.0101 (0.0389)

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin			Adj. Slope (Std. Error) ^a	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=520) (R ² =0.065)	≤18.6	15.595 (72)	15.629 (128)	15.713 (54)	0.0522 (0.0628)	0.969 ^b 0.406 ^c	RACE (p=0.115) CSMOK (p<0.001)
	>18.6	15.450 (58)	15.598 (131)	15.566 (77)			
h) Maximal (n=741) (R ² =0.083)	≤18.6	15.439 (106)	15.573 (191)	15.722 (83)	0.0964 (0.0425)	0.073 ^b 0.024 ^c	RACE (p=0.112) CSMOK (p<0.001)
	>18.6	15.795 (79)	15.553 (178)	15.633 (104)			

^aSlope and standard error based on hemoglobin versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest 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) RACE (p<0.001) CSMOK (p<0.001)
Unknown	345	15.451	Unknown vs. Background	-0.016 (-0.142,0.110)	0.808	
Low	195	15.525	Low vs. Background	0.058 (-0.098,0.214)	0.464	
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			Initial Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Abn. Low	Normal	Abn. High			
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) RACE (p=0.100) CSMOK (p<0.001)
	M vs. L ^a	0.99 (0.44,2.22)	0.983	
	H vs. L ^a	0.93 (0.32,2.74)	0.900	
	M vs. L ^b	2.09 (0.46,9.47)	0.341	
	H vs. L ^b	2.04 (0.29,14.15)	0.472	

^aAbnormal low contrasted with normal.

^bAbnormal 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)**

Assumption	Time (Yrs.)	Hemoglobin Category	Percent/(n) Current Dioxin			Current Dioxin Contrast	Est. Relative Risk (95% C.I.)	p-Value
			Low	Medium	High			
e) Minimal (n=520)	≤18.6	Abn. Low	4.2	0.0	1.9	C-by-T*		0.136
		Normal	95.8	98.4	98.2	Overall†		0.116
		Abn. High	0.0	1.6	0.0	M vs. L ^a	--	--
			(72)	(128)	(54)	H vs. L ^a	0.46 (0.05,4.19)	0.493 ^c
						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 (n=741)	≤18.6	Abn. Low	5.1	0.0	1.9	C-by-T*		0.006
		Normal	95.0	98.4	98.2	Overall†		0.012
		Abn. High	0.0	1.6	0.0	M vs. L ^a	--	--
			(198)	(128)	(54)	H vs. L ^a	0.39 (0.05,2.83)	0.349 ^c
						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

^aAbnormal low contrasted with normal.

^bAbnormal high contrasted with normal.

^cTest 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)	≤18.6	C-by-T*		0.334	RACE (p=0.006) CSMOK*PACKYR (p=0.007)	
		Overall†		0.446		
		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)	≤18.6	C-by-T*		0.043	RACE (p=0.015) CSMOK*PACKYR (p=0.010)
			Overall†		0.116	
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		

*Abnormal low contrasted with normal.

^bAbnormal high contrasted with normal.

^cTest 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			Contrast	Abnormal Low versus Normal		Abnormal High versus Normal	
		Abn. Low	Normal	Abn. High		Est. Relative Risk (95% C.I.)	p-Value	Est. Relative Risk (95% C.I.)	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		Abnormal High versus Normal		Covariate Remarks
			Adj. Relative Risk (95% C.I.)	p-Value	Adj. Relative Risk (95% C.I.)	p-Value	
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 - Log₂ (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 - Log₂ (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 $\text{time} \leq 18.6$; $p=0.989$ for $\text{time} > 18.6$).

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 - Log₂ (Initial Dioxin) - Unadjusted						
Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)^a	p-Value	
a) Minimal (n=520) (R ² =0.002)	Low	130	45.113	0.1183 (0.1138)	0.299	
	Medium	259	45.500			
	High	131	45.398			
b) Maximal (n=741) (R ² =0.004)	Low	185	44.982	0.1485 (0.0819)	0.070	
	Medium	370	45.331			
	High	186	45.515			
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)^a	p-Value	Covariate Remarks
c) Minimal (n=520) (R ² =0.063)	Low	130	45.160	0.1091 (0.1104)	0.324	CSMOK (p<0.001)
	Medium	259	45.462			
	High	131	45.427			
d) Maximal (n=741) (R ² =0.081)	Low	185	45.037	0.1278 (0.0788)	0.105	CSMOK (p<0.001)
	Medium	370	45.305			
	High	186	45.512			

^aSlope and standard error based on hematocrit versus log₂ 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 - Log₂ (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean/(n) Current Dioxin			Slope (Std. Error)^a	p-Value	
		Low	Medium	High			
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 - Log₂ (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin			Adj. Slope (Std. Error)^a	p-Value	Covariate Remarks
		Low	Medium	High			
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	

^aSlope and standard error based on hematocrit versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest 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 13-9. (Continued)
Analysis of Hematocrit (Percent)
(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	45.208	All Categories		0.428
Unknown	345	45.132	Unknown vs. Background	-0.075 (-0.460,0.309)	0.700
Low	195	45.336	Low vs. Background	0.128 (-0.347,0.604)	0.597
High	187	45.559	High vs. Background	0.351 (-0.132,0.835)	0.155
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	44.965**	All Categories		0.573**	DXCAT*AGE (p=0.025)
Unknown	345	44.792**	Unknown vs. Background	-0.173 (-0.539,0.193)**	0.355**	RACE (p=0.051)
Low	195	45.001**	Low vs. Background	0.035 (-0.417,0.488)**	0.878**	CSMOK
High	187	45.153**	High vs. Background	0.188 (-0.277,0.654)**	0.428**	(p<0.001)
Total	1,510		(R ² =0.106)			

**Categorized current dioxin-by-covariate interaction (0.01<p≤0.05); adjusted mean, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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

In the adjusted analysis, there was a significant interaction between categorized current dioxin and age (Table 13-9 [j]: $p=0.025$). To explore this interaction, age was divided into two categories: those participants born in or after 1942, and those born prior to 1942. The overall contrast in the younger age stratum showed a marginally significant difference in hematocrit percentage means among the four current dioxin categories (Appendix Table L-1: $p=0.091$). The means for the background, unknown, low, and high current dioxin categories were 45.044, 44.882, 44.516, and 45.536 percent. In the older age stratum, the test of the overall contrast was not significant ($p=0.268$).

After the categorized current dioxin-by-age interaction was removed from the adjusted model, the overall contrast was nonsignificant (Table 13-9 [j]: $p=0.573$).

Hematocrit (Discrete)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

There was no significant association exhibited between abnormally low hematocrit and initial dioxin in the unadjusted analysis under either the minimal or maximal assumption (Table 13-10 [a] and [b]: $p=0.943$ and $p=0.611$). After the model was adjusted for covariates, the association remained nonsignificant for both cohorts (Table 13-10 [c] and [d]: $p=0.910$ and $p=0.556$).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the interaction between current dioxin and time since tour was not significant for the unadjusted analysis of hematocrit in its discrete form (Table 13-10 [e] and [f]: $p=0.330$ and $p=0.277$, respectively). For the adjusted analysis, the interaction remained nonsignificant under both assumptions (Table 13-10 [g] and [h]: $p=0.358$ and $p=0.300$, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast in the unadjusted analysis showed no significant association between an abnormally low hematocrit percentage and the four current dioxin categories (Table 13-10 [i]: $p=0.634$). After adjusting the model for covariates, the association remained nonsignificant (Table 13-10 [j]: $p=0.774$).

Mean Corpuscular Volume (Continuous)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

MCV was not significantly associated with initial dioxin either under the minimal or under the maximal assumption in the unadjusted analysis (Table 13-11 [a] and [b]: $p=0.730$ and $p=0.737$, respectively).

In the adjusted analysis of the minimal cohort, there was a significant interaction between initial dioxin and lifetime cigarette smoking history (Table 13-11 [c]: $p=0.045$). To examine this interaction, lifetime cigarette smoking history was divided into three strata: Ranch Hands who never smoked, Ranch Hands whose pack-years did not exceed 10, and Ranch Hands with more than 10 pack-years. The association between MCV and initial

TABLE 13-10.
Analysis of Hematocrit
(Discrete)

Ranch Hands - Log₂ (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	1.5	0.98 (0.56,1.70)	0.943
	Medium	259	1.9		
	High	131	1.5		
b) Maximal (n=741)	Low	185	0.5	1.11 (0.74,1.68)	0.611
	Medium	370	2.2		
	High	186	1.1		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.)^a	p-Value	Covariate Remarks
c) Minimal (n=520)	1.03 (0.59,1.82)	0.910	RACE (p=0.108)
d) Maximal (n=741)	1.14 (0.75,1.73)	0.556	RACE (p=0.122) CSMOK (p=0.113)

^aRelative 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 13-10. (Continued)

**Analysis of Hematocrit
(Discrete)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal Low/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=520)	≤18.6	1.4 (72)	0.0 (128)	0.0 (54)	0.15 (0.00,17.41)	0.330 ^b 0.431 ^c
	>18.6	1.7 (58)	3.8 (131)	2.6 (77)	0.87 (0.48,1.58)	0.643 ^c
f) Maximal (n=741)	≤18.6	0.9 (106)	0.5 (191)	0.0 (83)	0.46 (0.08,2.63)	0.277 ^b 0.383 ^c
	>18.6	0.0 (79)	3.9 (178)	1.9 (104)	1.09 (0.70,1.69)	0.715 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=520)	≤18.6	0.14 (0.00,13.94)	0.358 ^b 0.402 ^c	AGE (p=0.129) CSMOK (p=0.149)
	>18.6	0.72 (0.36,1.42)	0.343 ^c	
h) Maximal (n=741)	≤18.6	0.47 (0.08,2.76)	0.300 ^b 0.403 ^c	RACE (p=0.145) CSMOK (p=0.124)
	>18.6	1.09 (0.69,1.72)	0.720 ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 13-10. (Continued)

**Analysis of Hematocrit
(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	2.0	All Categories		0.634
Unknown	345	1.5	Unknown vs. Background	0.70 (0.26,1.94)	0.498
Low	195	2.6	Low vs. Background	1.26 (0.46,3.49)	0.654
High	187	1.1	High vs. Background	0.52 (0.12,2.27)	0.384
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		0.774	AGE (p=0.100) RACE (p=0.013)
Unknown	345	Unknown vs. Background	0.75 (0.27,2.06)	0.571	
Low	195	Low vs. Background	1.27 (0.46,3.53)	0.649	
High	187	High vs. Background	0.62 (0.14,2.76)	0.531	
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.

TABLE 13-11.

**Analysis of Mean Corpuscular Volume (cubic micra)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted						
Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)^a	p-Value	
a) Minimal (n=520) (R ² <0.001)	Low	130	91.465	0.0621 (0.1799)	0.730	
	Medium	259	91.308			
	High	131	91.702			
b) Maximal (n=741) (R ² <0.001)	Low	185	91.712	-0.0424 (0.1261)	0.737	
	Medium	370	91.446			
	High	186	91.559			

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)^a	p-Value	Covariate Remarks
c) Minimal (n=520) (R ² =0.105)	Low	130	89.966**	0.1630 (0.1789)**	0.363**	INIT*PACKYR (p=0.045) CSMOK (p<0.001) AGE*RACE (p=0.020)
	Medium	259	89.901**			
	High	131	90.518**			
d) Maximal (n=741) (R ² =0.087)	Low	185	89.854	0.0303 (0.1240)	0.807	CSMOK (p<0.001) AGE*RACE (p=0.028)
	Medium	370	89.601			
	High	186	90.012			

^aSlope and standard error based on mean corpuscular volume versus log₂ dioxin.

**Log₂ (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 13-11. (Continued)

**Analysis of Mean Corpuscular Volume (cubic micra)
(Continuous)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Mean/(n) Current Dioxin			Slope (Std. Error) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=520) (R ² =0.004)	≤18.6	91.050 (72)	91.099 (128)	91.550 (54)	0.1380 (0.2930)	0.527 ^b 0.638 ^c
	>18.6	92.197 (58)	91.661 (131)	91.391 (77)	-0.1019 (0.2397)	0.671 ^c
f) Maximal (n=741) (R ² =0.005)	≤18.6	91.491 (106)	91.119 (191)	91.249 (83)	-0.0098 (0.1956)	0.564 ^b 0.960 ^c
	>18.6	92.429 (79)	91.855 (178)	91.386 (104)	-0.1606 (0.1730)	0.354 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin			Adj. Slope (Std. Error) ^a	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=520) (R ² =0.099)	≤18.6	89.665 (72)	89.681 (128)	90.490 (54)	0.2740 (0.2911)	0.538 ^b 0.347 ^c	CSMOK (p<0.001) AGE*RACE (p=0.017)
	>18.6	90.299 (58)	90.250 (131)	90.148 (77)	0.0509 (0.2364)	0.830 ^c	
h) Maximal (n=741) (R ² =0.089)	≤18.6	89.739 (106)	89.339 (191)	89.685 (83)	0.0495 (0.1921)	0.781 ^b 0.797 ^c	CSMOK (p<0.001) AGE*RACE (p=0.025)
	>18.6	90.209 (79)	89.937 (178)	89.770 (104)	-0.0204 (0.1702)	0.905 ^c	

^aSlope and standard error based on mean corpuscular volume versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest 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 13-11. (Continued)

**Analysis of Mean Corpuscular Volume (cubic micra)
(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	91.276	All Categories		0.277
Unknown	345	91.871	Unknown vs. Background	0.594 (-0.017,1.206)	0.057
Low	195	91.559	Low vs. Background	0.283 (-0.474,1.040)	0.463
High	187	91.325	High vs. Background	0.049 (-0.721,0.819)	0.901
Total	1,510		(R ² =0.003)		

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

Current Dioxin Category	n	Adj. Mean	Contrast	Difference of Adj. Means (95% C.I.)	p-Value	Covariate Remarks
Background	783	89.621	All Categories		0.653	RACE (p<0.001) AGE*CSMOK
Unknown	345	89.966	Unknown vs. Background	0.345 (-0.233,0.923)	0.242	(p=0.015)
Low	195	89.814	Low vs. Background	0.194 (-0.519,0.907)	0.595	AGE*PACKYR
High	187	89.898	High vs. Background	0.277 (-0.457,1.011)	0.460	(p=0.018) CSMOK*PACKYR
Total	1,510		(R ² =0.120)			(p=0.003)

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.

dioxin was nonsignificant in all three strata (Appendix Table L-1: 0 pack-years: $p=0.795$; $>0-10$ pack-years: $p=0.412$; >10 pack-years: $p=0.268$). However, the association was negative for those who never smoked (slope= -0.0831) and was positive for those who smoked ($>0-10$ pack-years: slope= 0.2841 ; >10 pack-years: slope= 0.2888). When this interaction was removed from the adjusted minimal analysis, the association between MCV and initial dioxin remained nonsignificant (Table 13-11 [c]: $p=0.363$). The association also remained nonsignificant for the adjusted maximal analysis (Table 13-11 [d]: $p=0.807$).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

In the unadjusted analysis of MCV, the current dioxin-by-time since tour interaction was not significant for both the minimal and the maximal cohorts (Table 13-11 [e] and [f]: $p=0.527$ and $p=0.564$). After adjusting for current cigarette smoking and an age-by-race interaction, the current dioxin-by-time since tour interaction remained nonsignificant for both cohorts (Table 13-11 [g] and [h]: $p=0.538$ and $p=0.781$, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The test for the overall contrast of the four current dioxin categories was not significant in the unadjusted analysis of MCV (Table 13-11 [i]: $p=0.277$). However, the mean MCV for the unknown category was marginally higher than the mean MCV for the background category ($p=0.057$). The MCV means for the background, unknown, low, and high categories were 91.276, 91.871, 91.559, and 91.325 cubic micra.

In the adjusted analysis of MCV, the overall contrast remained nonsignificant (Table 13-11 [j]: $p=0.653$). The difference between the unknown and background categories became nonsignificant with the inclusion of race, and the age-by-current cigarette smoking, age-by-lifetime cigarette smoking history, and current cigarette smoking-by-lifetime cigarette smoking history interactions in the model ($p=0.242$).

Mean Corpuscular Volume (Discrete)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

There was no significant association between abnormally high MCV and initial dioxin in the unadjusted analyses of the minimal and maximal cohorts (Table 13-12 [a] and [b]: $p=0.999$ and $p=0.179$, respectively).

In the adjusted analysis of the minimal cohort, there was a significant interaction between initial dioxin and lifetime cigarette smoking history (Table 13-12 [c]: $p=0.019$). To examine this interaction lifetime cigarette smoking history was divided into three strata: Ranch Hands who never smoked, Ranch Hands whose pack-years did not exceed 10, and Ranch Hands with more than 10 pack-years. The association between MCV and initial dioxin was not significant for all three strata (Appendix Table L-1: 0 pack-years: $p=0.416$; $>0-10$ pack-years: $p=0.712$; >10 pack-years: $p=0.568$). However, the risk of an abnormally high MCV increased as the amount of cigarettes smoked in one's lifetime increased. In particular, the risk was less than 1 for those who never smoked (Adj. RR= 0.61), and for those whose pack-years did not exceed 10 (Adj. RR= 0.92). The risk was greater than 1 for those with more than 10 pack-years (Adj. RR= 1.09). After this interaction was removed

TABLE 13-12.

**Analysis of Mean Corpuscular Volume
(Discrete)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)^a	p-Value
a) Minimal (n=520)	Low	130	11.5	1.00 (0.80,1.24)	0.999
	Medium	259	12.7		
	High	131	12.2		
b) Maximal (n=741)	Low	185	7.0	1.12 (0.95,1.32)	0.179
	Medium	370	12.7		
	High	186	10.8		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted			
Assumption	Adj. Relative Risk (95% C.I.)^a	p-Value	Covariate Remarks
c) Minimal (n=520)	1.00 (0.80,1.26)**	0.970**	INIT*PACKYR (p=0.019) CSMOK (p<0.001)
d) Maximal (n=741)	1.17 (0.98,1.39)**	0.087**	INIT*PACKYR (p=0.014) AGE (p=0.052) CSMOK*PACKYR (p=0.033)

^aRelative risk for a twofold increase in dioxin.

**Log₂ (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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 13-12. (Continued)
Analysis of Mean Corpuscular Volume
(Discrete)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=520)	≤18.6	9.7 (72)	13.3 (128)	11.1 (54)	0.99 (0.69,1.42)	0.999 ^b 0.960 ^c
	>18.6	13.8 (58)	13.0 (131)	11.7 (77)		0.99 (0.75,1.32)
f) Maximal (n=741)	≤18.6	6.6 (106)	13.1 (191)	8.4 (83)	1.15 (0.89,1.49)	0.808 ^b 0.288 ^c
	>18.6	7.6 (79)	13.5 (178)	10.6 (104)		1.10 (0.89,1.37)

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=520)	≤18.6	1.06 (0.71,1.58)	0.772 ^c	AGE (p=0.137) CSMOK*PACKYR (p=0.039)
	>18.6	1.06 (0.78,1.42)	0.724 ^c	
h) Maximal (n=741)	≤18.6	1.20 (0.91,1.59)	0.195 ^c	AGE (p=0.032) CSMOK*PACKYR (p=0.046)
	>18.6	1.19 (0.95,1.50)	0.127 ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 13-12. (Continued)
Analysis of Mean Corpuscular Volume
(Discrete)

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

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	9.8	All Categories		0.070
Unknown	345	8.7	Unknown vs. Background	0.87 (0.56,1.36)	0.548
Low	195	15.9	Low vs. Background	1.73 (1.10,2.72)	0.017
High	187	9.6	High vs. Background	0.98 (0.57,1.68)	0.931
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		0.034	RACE (p=0.102)
Unknown	345	Unknown vs. Background	0.77 (0.49,1.22)	0.267	AGE*PACKYR (p=0.023)
Low	195	Low vs. Background	1.77 (1.11,2.82)	0.017	CSMOK*PACKYR (p=0.009)
High	187	High vs. Background	1.12 (0.63,1.97)	0.702	
Total	1,510				

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

from the model, the association between MCV and initial dioxin remained nonsignificant (Table 13-12 [c]: $p=0.970$).

In the adjusted analysis of the maximal cohort, there was also a significant interaction between initial dioxin and lifetime cigarette smoking history (Table 13-12 [d]: $p=0.014$). In the strata containing Ranch Hands with less than 10 pack-years (0 pack-years and >0-10 pack-years) the risk of an abnormally high MCV was less than 1, but was nonsignificant for both strata (Appendix Table L-1: Adj. RR=0.92, $p=0.837$ for 0 pack-years; Adj. RR=0.95, $p=0.735$ for >0-10 pack-years).

For Ranch Hands with more than 10 pack-years, the risk was significantly greater than 1 (Adj. RR=1.30, $p=0.020$). The percentages of abnormally high MCV in this stratum were 5.5, 16.7, and 17.6 percent for the low, medium, and high levels of initial dioxin. When this interaction was removed from the adjusted model, the risk of an abnormally high MCV became marginally significant (Table 13-12 [d]: Adj. RR=1.17, $p=0.087$). The covariates that were retained in the model were age and the interaction between current cigarette smoking and lifetime cigarette smoking history.

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not significant in the unadjusted analysis of abnormally high MCV under either the minimal or the maximal assumption (Table 13-12 [e] and [f]: $p=0.999$ and $p=0.808$). After adjusting for covariates, this interaction remained nonsignificant under both assumptions (Table 13-12 [g] and [h]: $p=0.978$ and $p=0.972$, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The test on the unadjusted overall contrast showed a marginally significant difference in the percentage of abnormally high MCV among the four current dioxin categories (Table 13-12 [i]: $p=0.070$). The percentages for the background, unknown, low, and high current dioxin categories were 9.8, 8.7, 15.9, and 9.6 percent. The risk of an abnormally high MCV was significantly greater than 1 for the low versus background contrast (Est. RR=1.73, 95% C.I.: [1.10,2.72], $p=0.017$). The risk was less than 1, but nonsignificant, for the unknown versus background and the high versus background contrasts (unknown versus background: $p=0.548$; high versus background: $p=0.931$).

After the model for MCV was adjusted for covariates, the overall contrast became significant (Table 13-12 [j]: $p=0.034$). The risk for the low versus background contrast remained significantly greater than 1 (Adj. RR=1.77, 95% C.I.: [1.11,2.82], $p=0.017$) and the risks for the other two contrasts remained nonsignificant (unknown versus background: $p=0.267$; high versus background: $p=0.702$). Race, the interaction between age and lifetime cigarette smoking history, and the interaction between current cigarette smoking and lifetime cigarette smoking history were the covariates that were retained in the model.

Mean Corpuscular Hemoglobin (Continuous)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

The unadjusted analysis of the minimal cohort showed no significant association between MCH and initial dioxin (Table 13-13 [a]: $p=0.643$). The association was also nonsignificant for the analysis of the maximal cohort (Table 13-13 [b]: $p=0.674$).

When the model for the minimal analysis was adjusted for covariates, there was a significant interaction between initial dioxin and lifetime cigarette smoking history (Table 13-13 [c]: $p=0.015$). Lifetime cigarette smoking history was divided into three strata to examine this interaction (0 pack-years, >0-10 pack-years, and >10 pack-years). Within each of these strata the association between MCH and initial dioxin was not significant (Appendix Table L-1: 0 pack-years: $p=0.634$; >0-10 pack-years: $p=0.640$; >10 pack-years: $p=0.185$). However, the association was negative for Ranch Hands who never smoked (0 pack-years: slope=-0.0552), and was positive for those with a smoking history (>0-10 pack-years: slope=0.0585; >10 pack-years: slope=0.1251). After this interaction was removed from the model, the association between MCH and initial dioxin remained nonsignificant (Table 13-13 [c]: $p=0.449$).

The association between MCH and initial dioxin for the adjusted analysis of the maximal cohort remained nonsignificant (Table 13-13 [d]: $p=0.941$).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not significant in either the unadjusted analysis of the minimal cohort or the unadjusted analysis of the maximal cohort for MCH (Table 13-13 [e] and [f]: $p=0.497$ and $p=0.386$, respectively). After the models were adjusted for covariates, the current dioxin-by-time interaction remained nonsignificant in both analyses of MCH (Table 13-13 [g] and [h]: minimal, $p=0.531$; maximal, $p=0.567$).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

A marginally significant difference in the mean MCH among the four current dioxin categories was exhibited by the overall contrast (Table 13-13 [i]: $p=0.072$). The means corresponding to the background, unknown, low, and high categories were 31.633, 31.923, 31.814, and 31.678 micromicrograms. The means for the three Ranch Hand categories were all higher than the mean for the Comparisons in the background category. The unknown category had a significantly higher mean MCH than the background category (unknown versus background: $p=0.012$), and the means for the low and high categories were also larger than the background category, but the differences were not significant (low versus background: $p=0.203$; high versus background: $p=0.760$).

When age, race, and current cigarette smoking were included in the model, the overall contrast became nonsignificant (Table 13-13 [j]: $p=0.325$). The adjusted mean MCH for the unknown category remained larger than the adjusted mean for the background category, but the difference was only marginally significant (unknown versus background: $p=0.090$). The adjusted means for the low and high categories also remained larger than the background category, but not significantly (low versus background: $p=0.253$; high versus background: $p=0.496$).

TABLE 13-13.

**Analysis of Mean Corpuscular Hemoglobin (micromicrogram)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error) ^a	p-Value
a) Minimal (n=520) (R ² <0.001)	Low	130	31.736	0.0301 (0.0650)	0.643
	Medium	259	31.668		
	High	131	31.866		
b) Maximal (n=741) (R ² <0.001)	Low	185	31.864	-0.0193 (0.0458)	0.674
	Medium	370	31.737		
	High	186	31.779		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error) ^a	p-Value	Covariate Remarks
c) Minimal (n=520) (R ² =0.105)	Low	130	31.062**	0.0491 (0.0648)**	0.449**	INIT*PACKYR (p=0.015) CSMOK (p<0.001) AGE*RACE (p=0.015)
	Medium	259	31.012**			
	High	131	31.249**			
d) Maximal (n=741) (R ² =0.087)	Low	185	31.021	-0.0034 (0.0451)	0.941	CSMOK (p<0.001) AGE*RACE (p=0.047)
	Medium	370	30.930			
	High	186	31.024			

^aSlope and standard error based on mean corpuscular hemoglobin versus log₂ dioxin.

**Log₂ (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 13-13. (Continued)

**Analysis of Mean Corpuscular Hemoglobin (micromicrogram)
(Continuous)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Mean/(n) Current Dioxin			Slope (Std. Error) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=520) (R ² =0.002)	≤18.6	31.611 (72)	31.637 (128)	31.893 (54)	0.0710 (0.1060)	0.497 ^b 0.503 ^c
	>18.6	31.902 (58)	31.782 (131)	31.697 (77)	-0.0220 (0.0867)	0.800 ^c
f) Maximal (n=741) (R ² =0.004)	≤18.6	31.780 (106)	31.653 (191)	31.707 (83)	0.0134 (0.0711)	0.386 ^b 0.851 ^c
	>18.6	32.122 (79)	31.869 (178)	31.654 (104)	-0.0690 (0.0629)	0.273 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin			Adj. Slope (Std. Error) ^a	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=520) (R ² =0.094)	≤18.6	30.979 (72)	30.967 (128)	31.305 (54)	0.0968 (0.1055)	0.531 ^b 0.359 ^c	CSMOK (p<0.001) AGE*RACE (p=0.013)
	>18.6	31.098 (58)	31.144 (131)	31.080 (77)	0.0145 (0.0857)	0.865 ^c	
h) Maximal (n=741) (R ² =0.088)	≤18.6	30.978 (106)	30.853 (191)	30.928 (83)	0.0196 (0.0698)	0.567 ^b 0.779 ^c	CSMOK (p<0.001) AGE*RACE (p=0.043)
	>18.6	31.180 (79)	31.049 (178)	30.893 (104)	-0.0326 (0.0619)	0.599 ^c	

^aSlope and standard error based on mean corpuscular hemoglobin versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest 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 13-13. (Continued)

**Analysis of Mean Corpuscular Hemoglobin (micromicrogram)
(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	31.633	All Categories		0.072
Unknown	345	31.923	Unknown vs. Background	0.289 (0.065,0.513)	0.012
Low	195	31.814	Low vs. Background	0.180 (-0.097,0.458)	0.203
High	187	31.678	High vs. Background	0.044 (-0.238,0.326)	0.760
Total	1,510		(R ² =0.005)		

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	30.871	All Categories		0.325	AGE (p<0.001) RACE (p<0.001) CSMOK (p<0.001)
Unknown	345	31.055	Unknown vs. Background	0.184 (-0.028,0.397)	0.090	
Low	195	31.024	Low vs. Background	0.153 (-0.109,0.416)	0.253	
High	187	30.965	High vs. Background	0.094 (-0.176,0.364)	0.496	
Total	1,510		(R ² =0.111)			

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.

Mean Corpuscular Hemoglobin (Discrete)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

The association between MCH and initial dioxin was not significant for either the minimal or the maximal unadjusted analysis (Table 13-14 [a] and [b]: $p=0.404$ and $p=0.287$, respectively).

The association in the adjusted minimal analysis remained nonsignificant (Table 13-14 [c]: $p=0.376$). After adjusting the model in the maximal analysis for covariates, there was a significant interaction between initial dioxin and lifetime cigarette smoking history (Table 13-14 [d]: $p=0.016$). This interaction was examined by dividing lifetime cigarette smoking history into three strata (0 pack-years, >0-10 pack-years, and >10 pack-years). The association between MCH and initial dioxin was not significant within any of the three strata (Appendix Table L-1: 0 pack-years: $p=0.970$; >0-10 pack-years: $p=0.879$; >10 pack-years: $p=0.138$). However, the risk of abnormally high MCH was less than 1 for the strata containing Ranch Hands with fewer than 10 pack-years (0 pack-years: Adj. RR=0.99; >0-10 pack-years: Adj. RR=0.97), and was greater than 1 for those with more than 10 pack-years (Adj. RR=1.21). When this interaction was removed from the adjusted model, the association between MCH and initial dioxin remained nonsignificant (Table 13-14 [d]: $p=0.261$).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not significant in both the unadjusted minimal analysis and in the unadjusted maximal analysis of discretized MCH. (Table 13-14 [e] and [f]: $p=0.127$ and $p=0.301$, respectively). After adjusting the models for covariates, the interaction remained nonsignificant in both analyses of MCH in its discrete form (Table 13-14 [g] and [h]: $p=0.139$ and $p=0.382$).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast showed no significant difference in the percentage of abnormally high MCH levels among the four current dioxin categories (Table 13-14 [i]: $p=0.719$). After the model was adjusted for covariates, the contrast remained nonsignificant (Table 13-14 [j]: $p=0.628$).

Mean Corpuscular Hemoglobin Concentration (Continuous)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

The association between MCHC and initial dioxin was not significant in the unadjusted analysis of the minimal cohort or the maximal cohort (Table 13-15 [a] and [b]: $p=0.695$ and $p=0.670$).

There was a significant interaction between initial dioxin and age in the adjusted analysis of the minimal cohort (Table 13-15 [c]: $p=0.025$). To explore this interaction, the association between MCHC and initial dioxin was examined separately for Ranch Hands born in or after 1942 and for Ranch Hands born prior to 1942. The association was nonsignificant for both strata, but was negative for the younger Ranch Hands and positive for

TABLE 13-14.

**Analysis of Mean Corpuscular Hemoglobin
(Discrete)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)^a	p-Value
a) Minimal (n=520)	Low	130	6.2	1.11 (0.87,1.43)	0.404
	Medium	259	8.5		
	High	131	9.2		
b) Maximal (n=741)	Low	185	6.0	1.11 (0.92,1.34)	0.287
	Medium	370	8.4		
	High	186	8.1		
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.)^a	p-Value	Covariate Remarks		
c) Minimal (n=520)	1.13 (0.87,1.46)	0.376	CSMOK (p<0.001)		
d) Maximal (n=741)	1.12 (0.92,1.36)**	0.261**	INIT*PACKYR (p=0.016) CSMOK (p<0.001)		

^aRelative risk for a twofold increase in dioxin.

^{**}Log₂ (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted relative risk, confidence interval, and p-value derived from a model after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 13-14. (Continued)
Analysis of Mean Corpuscular Hemoglobin
(Discrete)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	<u>Percent Abnormal High/(n) Current Dioxin</u>			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=520)	≤18.6	2.8 (72)	7.8 (128)	9.3 (54)	1.41 (0.92,2.15)	0.127 ^b 0.112 ^c
	>18.6	13.8 (58)	8.4 (131)	7.8 (77)	0.92 (0.66,1.29)	0.645 ^c
f) Maximal (n=741)	≤18.6	5.7 (106)	6.3 (191)	8.4 (83)	1.24 (0.91,1.68)	0.301 ^b 0.176 ^c
	>18.6	7.6 (79)	10.7 (178)	6.7 (104)	1.00 (0.78,1.29)	0.992 ^c
Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted						
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a		p-Value	Covariate Remarks	
g) Minimal (n=520)	≤18.6	1.43 (0.92,2.23)		0.139 ^b 0.109 ^c	CSMOK (p<0.001)	
	>18.6	0.94 (0.67,1.32)		0.725 ^c		
h) Maximal (n=741)	≤18.6	1.29 (0.93,1.79)		0.382 ^b 0.124 ^c	AGE (p=0.129) CSMOK (p<0.001)	
	>18.6	1.08 (0.83,1.40)		0.585 ^c		

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 13-14. (Continued)

**Analysis of Mean Corpuscular Hemoglobin
(Discrete)**

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

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	6.8	All Categories		0.719
Unknown	345	7.3	Unknown vs. Background	1.08 (0.66,1.76)	0.771
Low	195	9.2	Low vs. Background	1.40 (0.80,2.45)	0.238
High	187	7.5	High vs. Background	1.11 (0.60,2.06)	0.728
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		0.628	AGE (p<0.001) RACE (p=0.150)
Unknown	345	Unknown vs. Background	0.97 (0.59,1.62)	0.918	CSMOK*PACKYR (p=0.038)
Low	195	Low vs. Background	1.38 (0.78,2.45)	0.267	
High	187	High vs. Background	1.28 (0.68,2.40)	0.451	
Total	1,510				

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

TABLE 13-15.

**Analysis of Mean Corpuscular Hemoglobin Concentration (gm/dl)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted						
Assumption	Initial Dioxin	n	Mean	Slope (Std. Error)^a	p-Value	
a) Minimal (n=520) (R ² <0.001)	Low	130	34.681	0.0077 (0.0197)		0.695
	Medium	259	34.656			
	High	131	34.720			
b) Maximal (n=741) (R ² <0.001)	Low	185	34.719	-0.0062 (0.0146)		0.670
	Medium	370	34.683			
	High	186	34.680			
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error)^a	p-Value	Covariate Remarks
c) Minimal (n=520) (R ² =0.060)	Low	130	34.516**	-0.0117 (0.0199)**	0.559**	INIT*AGE (p=0.025) RACE (p<0.001) PACKYR (p=0.036)
	Medium	259	34.471**			
	High	131	34.491**			
d) Maximal (n=741) (R ² =0.058)	Low	185	34.415	-0.0149 (0.0146)	0.306	AGE (p=0.015) RACE*PACKYR (p=0.050)
	Medium	370	34.417			
	High	186	34.356			

^aSlope and standard error based on mean corpuscular hemoglobin concentration versus log₂ dioxin.

**Log₂ (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 13-15. (Continued)

**Analysis of Mean Corpuscular Hemoglobin Concentration (gm/dl)
(Continuous)**

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Mean/(n) Current Dioxin			Slope (Std. Error) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=520) (R ² =0.009)	≤18.6	34.700 (72)	34.705 (128)	34.806 (54)	0.0200 (0.0320)	0.915 ^b 0.532 ^c
	>18.6	34.578 (58)	34.647 (131)	34.653 (77)	0.0156 (0.0261)	0.552 ^c
f) Maximal (n=741) (R ² =0.004)	≤18.6	34.711 (106)	34.720 (191)	34.714 (83)	0.0158 (0.0227)	0.316 ^b 0.487 ^c
	>18.6	34.732 (79)	34.666 (178)	34.612 (104)	-0.0146 (0.0201)	0.467 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin			Adj. Slope (Std. Error) ^a	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=520) (R ² =0.054)	≤18.6	34.537 (72)	34.506 (128)	34.555 (54)	-0.0055 (0.0324)	0.985 ^b 0.866 ^c	AGE (p=0.143) RACE (p<0.001) PACKYR (p=0.042)
	>18.6	34.426 (58)	34.479 (131)	34.447 (77)	-0.0047 (0.0264)	0.859 ^c	
h) Maximal (n=741) (R ² =0.055)	≤18.6	34.469 (106)	34.495 (191)	34.434 (83)	0.0024 (0.0227)	0.322 ^b 0.917 ^c	AGE (p=0.021) RACE (p<0.001) PACKYR
	>18.6	34.514 (79)	34.478 (178)	34.371 (104)	-0.0270 (0.0201)	0.179 ^c	(p=0.034)

^aSlope and standard error based on mean corpuscular hemoglobin concentration versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest 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 13-15. (Continued)

**Analysis of Mean Corpuscular Hemoglobin Concentration (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	34.629	All Categories		0.022
Unknown	345	34.723	Unknown vs. Background	0.094 (0.026,0.162)	0.007
Low	195	34.722	Low vs. Background	0.093 (0.009,0.178)	0.031
High	187	34.657	High vs. Background	0.029 (-0.058,0.115)	0.515
Total	1,510		(R ² =0.006)		

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	34.401	All Categories		0.029	RACE*CSMOK (p=0.029)
Unknown	345	34.484	Unknown vs. Background	0.083 (0.016,0.150)	0.016	CSMOK*PACKYR (p=0.034)
Low	195	34.497	Low vs. Background	0.095 (0.013,0.178)	0.024	
High	187	34.416	High vs. Background	0.015 (-0.069,0.099)	0.727	
Total	1,510		(R ² =0.059)			

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 older Ranch Hands (Appendix Table L-1: born \geq 1942: slope=-0.0394, p=0.158; born <1942: slope=0.0248, p=0.390). Without this interaction in the adjusted model, the association between MCHC and initial dioxin remained nonsignificant (Table 13-15 [c]: p=0.559).

After the model in the maximal analysis was adjusted for significant covariates, the association between MCHC and initial dioxin remained nonsignificant (Table 13-15 [d]: p=0.306).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

There was no significant interaction between current dioxin and time since tour in either the minimal or maximal analysis of MCHC (Table 13-15 [e] and [f]: p=0.915 and p=0.316, respectively). After the adjustment for covariate information was made, the interaction remained nonsignificant in both analyses (Table 13-15 [g] and [h]: p=0.985 and p=0.322, respectively).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The contrast of all four current dioxin categories showed a significant difference in the MCHC means (Table 13-15 [i]: p=0.022). In particular, the means for the unknown category and the low category were significantly greater than the mean for the background category (unknown versus background: p=0.007; low versus background: p=0.031). The mean for the high category was also greater than the mean for the background category, but the difference was not significant (high versus background: p=0.515). The means for the background, unknown, low, and high categories were 34.629, 34.723, 34.722, and 34.657 gm/dl.

In the adjusted analysis of MCHC, the overall contrast remained significant (Table 13-15 [j]: p=0.029). The unknown versus background and the low versus background contrasts also remained significant (unknown versus background: p=0.016; low versus background: p=0.024), and the high versus background contrast remained nonsignificant (high versus background: p=0.727).

Platelet Count (Continuous)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

In the unadjusted analysis of the minimal cohort, the association between platelet count and initial dioxin was not significant (Table 13-16 [a]: p=0.211). There was, however, a significant positive association in the analysis of the maximal cohort (Table 13-16 [b]: p=0.030). For this cohort, the mean platelet counts for the low, medium, and high levels of initial dioxin were 256.31, 264.41, and 268.39 thousand/mm³.

The association between platelet count and initial dioxin remained nonsignificant for the minimal cohort after the model was adjusted for significant covariates (Table 13-16 [c]: p=0.603). For the maximal cohort, the association became nonsignificant after the adjustment was made (Table 13-16 [d]: p=0.181). The covariates that were retained in the maximal analysis were the age-by-race and the age-by-lifetime cigarette smoking history interactions.

TABLE 13-16.

**Analysis of Platelet Count (thousand/mm³)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Mean	Slope (Std. Error) ^a	p-Value
a) Minimal (n=519) (R ² =0.003)	Low	129	254.24	2.638 (2.105)	0.211
	Medium	259	270.00		
	High	131	268.73		
b) Maximal (n=740) (R ² =0.006)	Low	185	256.31	3.252 (1.494)	0.030
	Medium	369	264.41		
	High	186	268.39		

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted

Assumption	Initial Dioxin	n	Adj. Mean	Adj. Slope (Std. Error) ^a	p-Value	Covariate Remarks
c) Minimal (n=519) (R ² =0.056)	Low	129	268.47	1.111 (2.133)	0.603	AGE*PACKYR (p=0.018) RACE*PACKYR (p=0.038)
	Medium	259	280.91			
	High	131	278.29			
d) Maximal (n=740) (R ² =0.045)	Low	185	261.90	2.020 (1.509)	0.181	AGE*RACE (p=0.044) AGE*PACKYR (p=0.016)
	Medium	369	269.32			
	High	186	270.23			

^aSlope and standard error based on platelet count versus log₂ 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 13-16. (Continued)
Analysis of Platelet Count (thousand/mm³)
(Continuous)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Mean/(n) Current Dioxin			Slope (Std. Error) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=519) (R ² =0.005)	≤18.6	251.86 (71)	267.44 (128)	267.17 (54)	4.167 (3.434)	0.491 ^b 0.226 ^c
	>18.6	269.40 (58)	267.63 (131)	268.88 (77)	1.114 (2.802)	0.691 ^c
f) Maximal (n=740) (R ² =0.007)	≤18.6	255.30 (106)	262.17 (190)	267.45 (83)	3.552 (2.321)	0.834 ^b 0.127 ^c
	>18.6	255.34 (79)	266.06 (178)	272.13 (104)	2.904 (2.052)	0.158 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean/(n) Current Dioxin			Adj. Slope (Std. Error) ^a	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=519) (R ² =0.059)	≤18.6	266.45 (71)	277.92 (128)	274.25 (54)	1.217 (3.476)	0.693 ^b 0.726 ^c	AGE*PACKYR (p=0.025) RACE*PACKYR (p=0.002)
	>18.6	284.64 (58)	278.45 (131)	279.75 (77)	-0.500 (2.830)	0.860 ^c	
h) Maximal (n=740) (R ² =0.045)	≤18.6	261.37 (106)	267.10 (190)	267.10 (83)	1.658 (2.341)	0.971 ^b 0.381 ^c	AGE*RACE (p=0.046) AGE*PACKYR (p=0.019)
	>18.6	261.62 (79)	270.56 (178)	274.38 (104)	1.768 (2.073)	0.394 ^c	

^aSlope and standard error based on platelet count versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest 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 13-16. (Continued)

**Analysis of Platelet Count (thousand/mm³)
(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	259.01	All Categories		0.083
Unknown	345	261.81	Unknown vs. Background	2.80 (-4.32,9.93)	0.440
Low	195	265.22	Low vs. Background	6.21 (-2.61,15.03)	0.168
High	187	270.05	High vs. Background	11.05 (2.08,20.02)	0.016
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	259.40**	All Categories		0.217**	DXCAT*AGE (p=0.031)
Unknown	345	262.07**	Unknown vs. Background	2.67 (-4.41,9.74)**	0.461**	CSMOK (p=0.067)
Low	195	265.00**	Low vs. Background	5.60 (-3.16,14.35)**	0.210**	PACKYR
High	187	268.16**	High vs. Background	8.76 (-0.24,17.76)**	0.057**	(p=0.004)
Total	1,510		(R ² =0.028)			

**Categorized current dioxin-by-covariate interaction (0.01 < p ≤ 0.05); adjusted mean, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

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

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

Under the minimal and maximal assumptions, the interaction between current dioxin and time since tour was not significant in the unadjusted analysis of platelet count (Table 13-16 [e] and [f]: $p=0.491$ and $p=0.834$, respectively). In the adjusted analysis, the interaction remained nonsignificant under both assumptions (Table 13-16 [g] and [h]: $p=0.693$ and $p=0.971$).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The contrast of all four current dioxin categories showed a marginally significant association between platelet count and current dioxin (Table 13-16 [i]: $p=0.083$). The mean platelet counts for the three Ranch Hand categories were greater than the mean platelet count for Comparisons in the background category. The means were 259.01 thousand/ mm^3 for the background category and 261.81, 265.22, and 270.05 thousand/ mm^3 for the unknown, low, and high categories. The differences in means between the unknown and background categories and between the low and background categories were not significant (unknown versus background: $p=0.440$; low versus background: $p=0.168$). But, the mean for the high category was significantly greater than the mean for the background category (high versus background: $p=0.016$).

In the adjusted model, there was a significant interaction between categorized current dioxin and age (Table 13-16 [j]: $p=0.031$). To examine this interaction, age was stratified into two categories: one containing those participants born in or after 1942, the other containing those born before 1942. Within the stratum containing the younger participants, there was a significant difference in mean platelet count among the four current dioxin categories (Appendix Table L-1: $p=0.010$). The adjusted means in this stratum were 263.06, 257.98, 271.16, and 279.94 thousand/ mm^3 for the background, unknown, low, and high categories. When contrasting the background category with the other three, the only significant difference in means was between the high and background categories (high versus background: $p=0.005$). The other two contrasts were nonsignificant (unknown versus background: $p=0.398$; low versus background: $p=0.242$). Within the stratum containing the older participants, there was no significant difference in mean platelet count among the four current dioxin categories ($p=0.435$). The adjusted means tended to increase over the current dioxin categories in the younger age stratum and tended to decrease in the older age stratum.

Without the categorized current dioxin-by-age interaction in the adjusted model, the overall contrast became nonsignificant (Table 13-16 [j]: $p=0.217$). Also, the difference between the mean platelet count for the high category and the mean for the background category became only marginally significant ($p=0.057$). The covariates that were retained in the model were age, current cigarette smoking, and lifetime cigarette smoking history.

Platelet Count (Discrete)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

There was no significant association between platelet count and initial dioxin for either the minimal or the maximal cohort in the unadjusted analysis (Table 13-17 [a] and [b]: $p=0.398$ and $p=0.133$, respectively). No covariates were retained in the adjusted model, therefore the results remained unchanged.

TABLE 13-17.
Analysis of Platelet Count
(Discrete)

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)^a	p-Value
a) Minimal (n=519)	Low	129	1.6	1.20 (0.80,1.80)	0.398
	Medium	259	3.5		
	High	131	2.3		
b) Maximal (n=740)	Low	185	0.5	1.28 (0.94,1.76)	0.133
	Medium	369	2.7		
	High	186	3.2		
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted					
Assumption			Adj. Relative Risk (95% C.I.)^a	p-Value	Covariate Remarks
c) Minimal (n=519)			1.20 (0.80,1.80)	0.398	- -
d) Maximal (n=740)			1.28 (0.94,1.76)	0.133	- -

^aRelative 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 13-17. (Continued)
Analysis of Platelet Count
(Discrete)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.)^a	p-Value
		Low	Medium	High		
e) Minimal (n=519)	≤18.6	0.0 (71)	3.9 (128)	0.0 (54)	0.90 (0.38,2.17)	0.551 ^b 0.820 ^c
	>18.6	3.5 (58)	3.1 (131)	3.9 (77)	1.22 (0.75,1.97)	0.428 ^c
f) Maximal (n=740)	≤18.6	0.0 (106)	2.6 (190)	1.2 (83)	1.19 (0.65,2.19)	0.930 ^b 0.573 ^c
	>18.6	2.5 (79)	2.3 (178)	4.8 (104)	1.23 (0.84,1.80)	0.291 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)^a	p-Value	Covariate Remarks
g) Minimal (n=519)	≤18.6	0.90 (0.38,2.17)	0.551 ^b 0.820 ^c	--
	>18.6	1.22 (0.75,1.97)	0.428 ^c	
h) Maximal (n=740)	≤18.6	1.19 (0.65,2.19)	0.930 ^b 0.573 ^c	--
	>18.6	1.23 (0.84,1.80)	0.292 ^c	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest 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 13-17. (Continued)

**Analysis of Platelet Count
(Discrete)**

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

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	1.2	All Categories		0.181
Unknown	345	2.3	Unknown vs. Background	2.04 (0.78,5.34)	0.145
Low	195	2.6	Low vs. Background	2.26 (0.75,6.83)	0.147
High	187	3.2	High vs. Background	2.85 (1.00,8.11)	0.050
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		0.181	- -
Unknown	345	Unknown vs. Background	2.04 (0.78,5.34)	0.145	
Low	195	Low vs. Background	2.26 (0.75,6.83)	0.147	
High	187	High vs. Background	2.85 (1.00,8.11)	0.050	
Total	1,510				

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

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

In the unadjusted analysis of platelet count in its discrete form, the interaction between current dioxin and time since tour was not significant for either the minimal or maximal cohort (Table 13-17 [e] and [f]: $p=0.551$ and $p=0.930$). There were no covariates retained in the adjusted model, thus the results remained unchanged.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall unadjusted contrast showed no significant differences in the percentage of abnormally high platelet counts across the four current dioxin categories (Table 13-17 [i]: $p=0.181$). However, the risk of an abnormally high platelet count was significantly greater than 1 when the high category was contrasted with the background category (Est. RR=2.85, 95% C.I.: [1.00,8.11], $p=0.050$).

The results in the adjusted model remained unchanged because there were no significant covariates retained in the model.

Prothrombin Time (Continuous)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

In the unadjusted analysis of prothrombin time in its continuous form, there was no significant association with initial dioxin under either assumption (Table 13-18 [a] and [b]: minimal assumption, $p=0.417$; maximal assumption, $p=0.444$).

In the adjusted model, a significant interaction between initial dioxin and lifetime cigarette smoking history was present under the minimal assumption (Table 13-18 [c]: $p=0.011$). To examine this interaction, lifetime cigarette smoking was divided into three strata (0 pack-years, >0-10 pack-years, and >10 pack-years). For Ranch Hands who had never smoked, the association between initial dioxin and prothrombin time was positive, but nonsignificant (Table L-1: $p=0.190$). For Ranch Hands who had less than 10 pack-years, the association between initial dioxin and prothrombin time was significantly positive ($p=0.001$). The adjusted mean prothrombin times, in this stratum, were 12.367, 12.320, and 12.334 seconds for the low, medium, and high initial dioxin categories. For Ranch Hands who had more than 10 pack-years, the association between initial dioxin and prothrombin time was negative but nonsignificant ($p=0.435$). Without this interaction in the model, there was a significant positive association between initial dioxin and prothrombin time (Table 13-18 [c]: $p=0.041$). The adjusted means increased over the low, medium, and high levels of initial dioxin (12.330, 12.347, and 12.416 seconds).

After adjusting the model under the maximal assumption for significant covariate information, the association between initial dioxin and prothrombin time remained nonsignificant (Table 13-18 [d]: $p=0.287$).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

In the unadjusted minimal and maximal analyses of prothrombin time, the interaction between current dioxin and time since tour was not significant (Table 13-18 [e] and [f]: $p=0.701$ and $p=0.653$, respectively).

TABLE 13-18.

**Analysis of Prothrombin Time (Seconds)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted						
Assumption	Initial Dioxin	n	Mean^a	Slope (Std. Error)^b	p-Value	
a) Minimal (n=519) (R ² =0.001)	Low	130	12.266	0.0013 (0.0015)	0.417	
	Medium	258	12.230			
	High	131	12.290			
b) Maximal (n=740) (R ² <0.001)	Low	185	12.241	0.0009 (0.0011)	0.444	
	Medium	370	12.231			
	High	185	12.267			

Ranch Hands - Log₂ (Initial Dioxin) - Adjusted						
Assumption	Initial Dioxin	n	Adj. Mean^a	Adj. Slope (Std. Error)^b	p-Value	Covariate Remarks
c) Minimal (n=513) (R ² =0.108)	Low	130	12.330**	0.0032 (0.0016)**	0.041**	INIT*PACKYR (p=0.011) RACE (p=0.005) AGE*CSMOK (p=0.037) CSMOK*DRKYR (p=0.025) PACKYR*DRKYR (p=0.003)
	Medium	254	12.347**			
	High	129	12.416**			
d) Maximal (n=731) (R ² =0.071)	Low	183	12.343	0.0012 (0.0012)	0.287	RACE (p=0.020) AGE*CSMOK (p=0.003) AGE*PACKYR (p<0.001) CSMOK*DRKYR (p=0.025)
	Medium	367	12.320			
	High	181	12.368			

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm prothrombin time versus log₂ dioxin.

**Log₂ (initial dioxin)-by-covariate interaction (0.01<p≤0.05); adjusted mean, adjusted slope, standard error, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 13-18. (Continued)
Analysis of Prothrombin Time (Seconds)
(Continuous)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted							
Assumption	Time (Yrs.)	Mean ^a /(n) Current Dioxin			Slope (Std. Error) ^b	p-Value	
		Low	Medium	High			
e) Minimal (n=519) (R ² =0.006)	≤18.6	12.260 (72)	12.186 (128)	12.206 (54)	0.0016 (0.0025)	0.701 ^c 0.536 ^d	
	>18.6	12.265 (58)	12.291 (130)	12.292 (77)	0.0003 (0.0021)	0.880 ^d	
f) Maximal (n=740) (R ² =0.003)	≤18.6	12.244 (106)	12.181 (191)	12.267 (83)	0.0002 (0.0018)	0.653 ^c 0.895 ^d	
	>18.6	12.198 (79)	12.277 (178)	12.312 (103)	0.0013 (0.0016)	0.408 ^d	

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted							
Assumption	Time (Yrs.)	Adj. Mean ^a /(n) Current Dioxin			Adj. Slope (Std. Error) ^b	p-Value	Covariate Remarks
		Low	Medium	High			
g) Minimal (n=513) (R ² =0.103)	≤18.6	12.330 (72)	12.299 (127)	12.342 (53)	0.0036 (0.0025)	0.713 ^c 0.153 ^d	RACE (p=0.015) AGE*CSMOK (p=0.003)
	>18.6	12.299 (58)	12.387 (127)	12.404 (76)	0.0024 (0.0021)	0.246 ^d	AGE*PACKYR (p<0.001) CSMOK*DRKYR (p=0.021)
h) Maximal (n=731) (R ² =0.085)	≤18.6	**** (105)	**** (190)	**** (81)	****	****	CURR*TIME*CSMOK (p=0.006) RACE (p=0.019)
	>18.6	**** (78)	**** (176)	**** (101)	****	****	AGE*CSMOK (p=0.007) AGE*PACKYR (p<0.001) CSMOK*DRKYR (p=0.024)

^aTransformed from natural logarithm scale.

^bSlope and standard error based on natural logarithm prothrombin time versus log₂ dioxin.

^cTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^dTest of significance for slope equal to 0 (current dioxin continuous, time categorized).

****Log₂ (current dioxin)-by-time-by-covariate interaction (p≤0.01); adjusted mean, adjusted slope, standard error, and p-value not presented.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 13-18. (Continued)
Analysis of Prothrombin Time (Seconds)
(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	785	12.256	All Categories		0.305
Unknown	345	12.219	Unknown vs. Background	-0.037 --	0.278
Low	195	12.207	Low vs. Background	-0.049 --	0.247
High	186	12.292	High vs. Background	0.036 --	0.409
Total	1,511		(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	785	****	All Categories		****	DXCAT*AGE (p=0.004)
Unknown	345	****	Unknown vs. Background	****	****	RACE (p<0.001)
Low	195	****	Low vs. Background	****	****	CSMOK (p<0.001)
High	186	****	High vs. Background	****	****	
Total	1,511		(R ² =0.050)			

^aTransformed from natural logarithm scale.

^cDifference of means after transformation to original scale; confidence interval on difference of means not given because analysis was performed on natural logarithm scale.

^fP-value is based on difference of means on natural logarithm scale.

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

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

The current dioxin-by-time interaction remained nonsignificant in the adjusted minimal analysis (Table 13-18 [g]: $p=0.713$). Under the maximal assumption, a significant interaction was present among current dioxin, time, and current cigarette smoking (Table 13-18 [h]: $p=0.006$). Current cigarette smoking was then stratified into four categories (never smoked, formerly smoked, smoked less than 20 cigarettes/day, and smoked more than 20 cigarettes/day) to investigate this interaction. The interaction between current dioxin and time was nonsignificant in all four strata (Table L-1: 0-never: $p=0.657$; 0-former: $p=0.131$; >0-20 cigarettes/day: $p=0.396$; >20 cigarettes/day: $p=0.107$). However, for former smokers, there was a marginally significant positive association between current dioxin and prothrombin time when time exceeded 18.6 years ($p=0.068$). There was also a marginally significant positive association between current dioxin and prothrombin time when time did not exceed 18.6 years for Ranch Hands who smoked less than 20 cigarettes per day ($p=0.082$). For nonsmokers (0-never and 0-former), the association between current dioxin and prothrombin time was negative in the later tour stratum (time \leq 18.6 years) and positive in the earlier tour stratum (time $>$ 18.6 years). In contrast, for the other two current smoking categories (>0-20 cigarettes/day and >20 cigarettes/day), the association was stronger in the later tour stratum than in the earlier tour stratum.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of prothrombin time, the overall comparison of the four current dioxin categories was nonsignificant (Table 13-18 [i]: $p=0.305$).

In the adjusted analysis of prothrombin time, there was a significant interaction between categorized current dioxin and age (Table 13-18 [j]: $p=0.004$). For the younger participants (born \geq 1942), the adjusted mean prothrombin times differed significantly (Appendix Table L-1: $p=0.045$). The adjusted means for the background, unknown, low, and high current dioxin categories were 12.402, 12.487, 12.272, and 12.395 seconds. The adjusted mean prothrombin time in the low current dioxin category was significantly less than the adjusted mean in the background category ($p=0.046$). For the older participants (born $<$ 1942), there was a marginally significant difference among the current dioxin categories ($p=0.082$). Within this stratum, the adjusted mean prothrombin times were 12.323, 12.263, 12.356, and 12.434 seconds for the background, unknown, low, and high current dioxin categories. There was also a marginally significant difference between the adjusted mean in the unknown category and the adjusted mean in the background category ($p=0.100$).

Prothrombin Time (Discrete)

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

The unadjusted analysis of prothrombin time in its discrete form showed no significant association with initial dioxin under either the minimal or the maximal assumption (Table 13-19 [a] and [b]: $p=0.722$ and $p=0.924$). The association between initial dioxin and prothrombin time remained nonsignificant after the models were adjusted for covariate information (Table 13-19 [c] and [d]: minimal assumption, $p=0.245$; maximal assumption, $p=0.789$).

TABLE 13-19.
Analysis of Prothrombin Time
(Discrete)

Ranch Hands - Log₂ (Initial Dioxin) - Unadjusted					
Assumption	Initial Dioxin	n	Percent Abnormal High	Est. Relative Risk (95% C.I.)^a	p-Value
a) Minimal (n=519)	Low	130	2.3	1.08 (0.71,1.65)	0.722
	Medium	258	3.5		
	High	131	1.5		
b) Maximal (n=740)	Low	185	3.2	0.98 (0.72,1.35)	0.924
	Medium	370	2.4		
	High	185	3.2		
Ranch Hands - Log₂ (Initial Dioxin) - Adjusted					
Assumption	Adj. Relative Risk (95% C.I.)^a		p-Value	Covariate Remarks	
c) Minimal (n=519)	1.31 (0.85,2.02)		0.245	RACE (p=0.093) AGE*CSMOK (p=0.045)	
d) Maximal (n=740)	1.05 (0.75,1.47)		0.789	RACE (p=0.083) AGE*PACKYR (p=0.005)	

^aRelative 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 13-19. (Continued)
Analysis of Prothrombin Time
(Discrete)

Ranch Hands - Log₂ (Current Dioxin) and Time - Unadjusted						
Assumption	Time (Yrs.)	Percent Abnormal High/(n) Current Dioxin			Est. Relative Risk (95% C.I.) ^a	p-Value
		Low	Medium	High		
e) Minimal (n=519)	≤18.6	1.4 (72)	2.3 (128)	1.9 (54)	1.48 (0.71,3.10)	0.300 ^b 0.299 ^c
	>18.6	3.5 (58)	4.6 (130)	1.3 (77)	0.91 (0.52,1.57)	0.724 ^c
f) Maximal (n=740)	≤18.6	3.8 (106)	0.5 (191)	4.8 (83)	1.01 (0.60,1.73)	0.889 ^b 0.957 ^c
	>18.6	3.8 (79)	2.8 (178)	3.9 (103)	0.97 (0.64,1.46)	0.873 ^c

Ranch Hands - Log₂ (Current Dioxin) and Time - Adjusted				
Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.) ^a	p-Value	Covariate Remarks
g) Minimal (n=519)	≤18.6	2.79 (1.13,6.88)	0.089 ^b 0.026 ^c	RACE (p=0.086) AGE*CSMOK (p=0.026) AGE*PACKYR (p=0.039)
	>18.6	1.14 (0.65,2.01)	0.652 ^c	
h) Maximal (n=740)	≤18.6	****	****	CURR*TIME*RACE (p=0.006) AGE*PACKYR (p=0.005)
	>18.6	****	****	

^aRelative risk for a twofold increase in dioxin.

^bTest of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

^cTest of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

****Log₂ (current dioxin)-by-time-by-covariate interaction (p≤0.01); adjusted relative risk, confidence interval, and p-value not presented.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 13-19. (Continued)

**Analysis of Prothrombin Time
(Discrete)**

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

Current Dioxin Category	n	Percent Abnormal High	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	785	4.7	All Categories		0.153
Unknown	345	3.5	Unknown vs. Background	0.73 (0.38,1.41)	0.350
Low	195	1.5	Low vs. Background	0.32 (0.10,1.04)	0.057
High	186	4.3	High vs. Background	0.91 (0.42,1.99)	0.810
Total	1,511				

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	785	All Categories		****	DXCAT*AGE (p=0.005) DXCAT*CSMOK
Unknown	345	Unknown vs. Background	****	****	(p=0.028)
Low	195	Low vs. Background	****	****	RACE (p=0.003)
High	186	High vs. Background	****	****	
Total	1,511				

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

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

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

In the unadjusted analysis of prothrombin time, the interaction between current dioxin and time since tour was not significant under the minimal and maximal assumptions (Table 13-19 [e] and [f]: $p=0.300$ and $p=0.889$).

After adjusting the model in the minimal analysis for race, age-by-current cigarette smoking, and age-by-lifetime cigarette smoking history, the interaction between current dioxin and time was marginally significant (Table 13-19 [g]: $p=0.089$). For time less than or equal to 18.6 years, there was a significant positive risk of an abnormally high prothrombin time (Adj. RR=2.79, $p=0.026$). The percentages of abnormalities in this stratum were 1.4, 2.3, and 1.9 percent for low, medium, and high levels of current dioxin. For time greater than 18.6 years, the risk was not significant ($p=0.652$).

In the adjusted maximal analysis, there was a significant interaction among current dioxin, time, and race (Table 13-19 [h]: $p=0.006$). The current dioxin-by-time interaction was not evaluated for Black Ranch Hands because there was only one abnormality for time less than or equal to 18.6 years. The abnormality was in the low current dioxin category. For time greater than 18.6 years, the risk of an abnormally high prothrombin time was not significant (Appendix Table L-1: $p=0.516$). However, there were only two abnormalities within this stratum; one in the medium current dioxin category and one in the high current dioxin category. In the non-Black stratum, the current dioxin-by-time interaction was not significant ($p=0.445$). This current dioxin-by-time-by-race interaction could have been caused by, or affected by, the sparse number of abnormalities in the Black stratum.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of prothrombin time, the overall contrast of the current dioxin categories was not significant (Table 13-19 [i]: $p=0.153$). However, for the low versus background contrast, the risk of an abnormally high prothrombin time was marginally less than 1 (Est. RR=0.32, 95% C.I.: [0.10,1.04], $p=0.057$).

In the adjusted analysis of prothrombin time, there was a significant interaction between categorized current dioxin and age (Table 13-19 [j]: $p=0.005$) and between categorized current dioxin and current cigarette smoking ($p=0.028$). To investigate these interactions, age was divided into two strata (born in or after 1942 and born before 1942); current cigarette smoking was divided into three strata (never smoked, formerly smoked, and currently smoked). Among the six combinations of these strata, the overall contrast of the current dioxin categories was significant only for the younger participants who had never smoked (Appendix Table L-1: $p=0.041$) and was marginally significant for the older participants who currently smoked ($p=0.093$). For the younger participants who had never smoked, the percentages of abnormal prothrombin times were 5.2, 13.9, 0.0, and 2.9 percent for the background, unknown, low, and high current dioxin categories. Also in this stratum, the risk of an abnormally high prothrombin time was marginally greater than 1 under the unknown versus background contrast (Adj. RR=3.38, 95% C.I.: [0.90,12.73], $p=0.072$). For the older participants who currently smoked, there were only five abnormalities in the background current dioxin category, one abnormality in the high category, and no abnormalities in the unknown and low categories.

Longitudinal Analysis

Laboratory Examination Variables

Longitudinal analyses were conducted for three hematology variables: MCV, MCH, and platelet count. For a specific longitudinal analysis (e.g., minimal assumption, initial dioxin analysis on MCV), the left side of each subpanel of a table provides the means and sample sizes for participants with MCV values at each examination. Based on the difference between 1987 MCV and 1982 MCV, the right side of each subpanel presents slopes, standard errors, and associated p-values (for models using initial dioxin or models using current dioxin and time since tour), or differences of examination mean changes, 95 percent confidence intervals, and associated p-values (for models using categorized current dioxin). The reported statistics are presented subject to the constraint that participants were compliant at both the 1982 and 1987 examinations.

Mean Corpuscular Volume (Continuous)

For the hematologic assessment, differences in MCV levels (cubic micra) between the 1982 Baseline examination and the 1987 examination were analyzed for associations with initial dioxin, current dioxin and time since tour, and categorized current dioxin. All analyses were conducted without adjustment for covariate information (Table 13-20).

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

The longitudinal analysis of the change in MCV levels from the 1982 Baseline examination to the 1987 examination displayed a nonsignificant positive association with initial dioxin under both the minimal and the maximal assumptions (Table 13-20 [a] and [b]: $p=0.116$ and $p=0.545$).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

Under both the minimal and the maximal assumptions, the longitudinal analysis of the difference between the 1982 and 1987 MCV levels exhibited a nonsignificant interaction between current dioxin and time since tour (Table 13-20 [c] and [d]: $p=0.327$ and $p=0.424$, respectively). However, for Ranch Hands in the minimal cohort with less than or equal to 18.6 years since tour, the longitudinal analysis detected a marginally significant positive association between current dioxin and the change in MCV levels from 1982 to 1987 (Table 13-20 [c]: $p=0.082$). The differences in the 1982 and 1987 MCV levels for this stratum were 1.583, 3.075, and 3.631 cubic micra for the low, medium, and high current dioxin categories.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the longitudinal analysis of the difference in MCV values between the 1982 Baseline examination and the 1987 examination, the overall contrast of the four current dioxin categories was not significant (Table 13-20 [e]: $p=0.453$).

Mean Corpuscular Hemoglobin (Continuous)

Longitudinal analyses were conducted to examine the change in the MCH levels (micromicrogram) of the study participants between the 1982 Baseline and 1987 examinations in relation to initial dioxin, current dioxin and time since tour, and current dioxin

TABLE 13-20.

**Longitudinal Analysis of Mean Corpuscular Volume (cubic micra)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin)						
Assumption	Initial Dioxin	Mean/(n) Examination			Slope (Std. Error)^a	p-Value
		1982	1985	1987		
a) Minimal (R ² =0.005)	Low	89.694 (124)	92.536 (121)	91.480 (124)	0.2688 (0.1707)	0.116
	Medium	88.413 (254)	92.275 (249)	91.322 (254)		
	High	88.629 (124)	92.827 (122)	91.782 (124)		
b) Maximal (R ² <0.001)	Low	88.735 (170)	92.767 (167)	91.748 (170)	0.0725 (0.1196)	0.545
	Medium	89.008 (358)	92.460 (350)	91.493 (358)		
	High	88.489 (178)	92.710 (175)	91.589 (178)		

^aSlope and standard error based on difference between 1987 mean corpuscular volume and 1982 mean corpuscular volume versus log₂ dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 13-20. (Continued)
Longitudinal Analysis of Mean Corpuscular Volume (cubic micra)
(Continuous)

Ranch Hands - Log₂ (Current Dioxin) and Time							
Assumption	Time (Yrs.)	Examination	Mean/(n) Current Dioxin			Slope (Std. Error)^a	p-Value
			Low	Medium	High		
c) Minimal (R ² =0.007)	≤18.6	1982	89.478 (69)	88.048 (125)	87.961 (51)	0.4851 (0.2781)	0.327 ^b 0.082 ^c
		1985	92.170 (67)	91.966 (122)	92.810 (50)		
		1987	91.061 (69)	91.123 (125)	91.592 (51)		
	>18.6	1982	90.127 (55)	88.876 (129)	88.781 (73)	0.1327 (0.2275)	0.560 ^c
		1985	93.370 (54)	92.598 (127)	92.506 (72)		
		1987	92.235 (55)	91.667 (129)	91.475 (73)		
d) Maximal (R ² =0.002)	≤18.6	1982	88.489 (94)	88.541 (185)	88.127 (79)	0.1895 (0.1870)	0.424 ^b 0.311 ^c
		1985	92.467 (91)	92.084 (180)	92.428 (78)		
		1987	91.478 (94)	91.168 (185)	91.215 (79)		
	>18.6	1982	89.224 (76)	89.419 (172)	88.800 (100)	-0.0091 (0.1628)	0.956 ^c
		1985	93.507 (75)	92.957 (170)	92.477 (98)		
		1987	92.557 (76)	91.887 (172)	91.447 (100)		

^aSlope and standard error based on difference between 1987 mean corpuscular volume and 1982 mean corpuscular volume versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest of significance for slope equal to 0 (current dioxin continuous, time categorized).

Note: **Minimal**--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 13-20. (Continued)

**Longitudinal Analysis of Mean Corpuscular Volume (cubic micra)
(Continuous)**

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Mean/(n) Examination			Contrast	Difference of Examination Mean Change (95% C.I.)	p-Value
	1982	1985	1987			
Background	88.604 (681)	92.303 (676)	91.230 (681)	All Categories		0.453
Unknown	88.971 (315)	92.761 (310)	91.830 (315)	Unknown vs. Background	0.232 (-0.328,0.792)	0.417
Low	88.445 (191)	92.428 (188)	91.604 (191)	Low vs. Background	0.533 (-0.140,1.206)	0.121
High	88.503 (179)	92.455 (176)	91.345 (179)	High vs. Background	0.216 (-0.474,0.906)	0.540

(R²=0.002)

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

categorized within group. The results of the longitudinal analyses (unadjusted for covariate information) are presented in Table 13-21.

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

The longitudinal analysis did not detect a significant association between initial dioxin and the change in MCH (as measured by the difference between the 1987 examination value and the 1982 examination value) under either the minimal or the maximal assumption (Table 13-21 [a] and [b]: $p=0.107$ and $p=0.982$).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

Under both the minimal and the maximal assumptions, the longitudinal analysis of the change in MCH between the 1982 Baseline examination and the 1987 examination exhibited a nonsignificant current dioxin-by-time since tour interaction (Table 13-21 [c] and [d]: $p=0.829$ and $p=0.623$, respectively). Thus, the difference between the 1982 and 1987 MCH levels did not differ significantly for the two time strata under either assumption.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The change in MCH levels between the 1982 Baseline examination and the 1987 examination did not differ significantly among the four current dioxin categories (Table 13-21 [e]: $p=0.609$).

Platelet Count (Continuous)

Longitudinal differences in platelet count (thousand/mm³) between the 1982 Baseline examination and the 1987 examination were analyzed to examine associations with initial dioxin in Ranch Hands, current dioxin and time since tour in Ranch Hands, and categorized current dioxin in Ranch Hands and Comparisons. Table 13-22 presents the results of these analyses.

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

The longitudinal analysis of the change in platelet count between 1982 and 1987 detected a negative association with initial dioxin for both the minimal and the maximal cohorts. However, the association was nonsignificant under both assumptions (Table 13-22 [a] and [b]: $p=0.553$ and $p=0.768$, respectively).

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

In the longitudinal analysis of the change in platelet count between the 1982 Baseline examination and the 1987 examination with current dioxin and time since tour, the interaction between current dioxin and time since tour was nonsignificant under both the minimal and the maximal assumptions (Table 13-22 [c] and [d]: $p=0.257$ and $p=0.789$). Thus, the association between current dioxin and the change in platelet count, 1987 relative to 1982, did not differ for the two time strata under either the minimal or the maximal assumption.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The simultaneous contrast of the four current dioxin categories was not significant in the longitudinal analysis of the change in mean platelet count between the 1982 Baseline and 1987 examinations (Table 13-22 [e]: $p=0.181$). However, the individual contrast of the

TABLE 13-21.

Longitudinal Analysis of Mean Corpuscular Hemoglobin (micromicrogram)
(Continuous)

Ranch Hands - Log ₂ (Initial Dioxin)						
Assumption	Initial Dioxin	Mean/(n) Examination			Slope (Std. Error) ^a	p-Value
		1982	1985	1987		
a) Minimal (R ² =0.005)	Low	30.998 (124)	31.483 (121)	31.734 (124)	0.0738 (0.0456)	0.107
	Medium	30.711 (254)	31.446 (249)	31.665 (254)		
	High	30.833 (124)	31.691 (122)	31.907 (124)		
b) Maximal (R ² <0.001)	Low	30.776 (170)	31.652 (167)	31.859 (170)	-0.0007 (0.0333)	0.982
	Medium	30.835 (358)	31.490 (350)	31.745 (358)		
	High	30.787 (178)	31.631 (175)	31.793 (178)		

^aSlope and standard error based on difference between 1987 mean corpuscular hemoglobin and 1982 mean corpuscular hemoglobin versus log₂ dioxin.

Note: **Minimal**--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.

Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 13-21. (Continued)

Longitudinal Analysis of Mean Corpuscular Hemoglobin (micromicrogram)
(Continuous)

Ranch Hands - Log ₂ (Current Dioxin) and Time							
Assumption	Time (Yrs.)	Examination	Mean/(n) Current Dioxin			Slope (Std. Error) ^a	p-Value
			Low	Medium	High		
c) Minimal (R ² =0.004)	≤18.6	1982	30.915 (69)	30.629 (125)	30.845 (51)	0.0572 (0.0745)	0.829 ^b 0.443 ^c
		1985	31.460 (67)	31.379 (122)	31.726 (50)		
		1987	31.609 (69)	31.634 (125)	31.914 (51)		
	>18.6	1982	31.140 (55)	30.824 (129)	30.738 (73)	0.0780 (0.0609)	0.201 ^c
		1985	31.657 (54)	31.503 (127)	31.569 (72)		
		1987	31.902 (55)	31.779 (129)	31.744 (73)		
d) Maximal (R ² <0.001)	≤18.6	1982	30.600 (94)	30.712 (185)	30.825 (79)	-0.0214 (0.0521)	0.623 ^b 0.682 ^c
		1985	31.559 (91)	31.425 (180)	31.582 (78)		
		1987	31.748 (94)	31.667 (185)	31.689 (79)		
	>18.6	1982	31.042 (76)	30.960 (172)	30.732 (100)	0.0126 (0.0454)	0.781 ^c
		1985	31.861 (75)	31.619 (170)	31.493 (98)		
		1987	32.150 (76)	31.871 (172)	31.686 (100)		

^aSlope and standard error based on difference between 1987 mean corpuscular hemoglobin and 1982 mean corpuscular hemoglobin versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest of significance for slope equal to 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 13-21. (Continued)

**Longitudinal Analysis of Mean Corpuscular Hemoglobin (micromicrogram)
(Continuous)**

e) Ranch Hands and Comparisons by Current Dioxin Category						
Current Dioxin Category	Mean/(n) Examination			Contrast	Difference of Examination Mean Change (95% C.I.) p-Value	
	1982	1985	1987			p-Value
Background	30.612 (681)	31.414 (676)	31.614 (681)	All Categories		0.609
Unknown	30.858 (315)	31.640 (310)	31.896 (315)	Unknown vs. Background	0.036 (-0.131,0.204)	0.671
Low	30.744 (191)	31.513 (188)	31.824 (191)	Low vs. Background	0.078 (-0.123,0.280)	0.447
High	30.773 (179)	31.532 (176)	31.687 (179)	High vs. Background	-0.088 (-0.295,0.119)	0.406
(R²=0.001)						

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

TABLE 13-22.

**Longitudinal Analysis of Platelet Count (thousand/cubic mm)
(Continuous)**

Ranch Hands - Log₂ (Initial Dioxin)						
Assumption	Initial Dioxin	Mean/(n) Examination			Slope (Std. Error)^a	p-Value
		1982	1985	1987		
a) Minimal (R ² <0.001)	Low	266.00 (123)	263.85 (120)	253.59 (123)	-0.971 (1.634)	0.553
	Medium	281.34 (254)	273.18 (249)	270.02 (254)		
	High	282.09 (124)	274.16 (122)	268.32 (124)		
b) Maximal (R ² <0.001)	Low	273.15 (170)	265.02 (167)	256.06 (170)	-0.359 (1.215)	0.768
	Medium	273.26 (357)	269.14 (348)	264.02 (357)		
	High	281.45 (178)	272.40 (175)	268.08 (178)		

^aSlope and standard error based on difference between 1987 platelet count and 1982 platelet count versus log₂ dioxin.
 Note: **Minimal**--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
 Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 13-22. (Continued)

Longitudinal Analysis of Platelet Count (thousand/cubic mm)
(Continuous)

Assumption	Time (Yrs.)	Examination	Mean/(n) Current Dioxin			Slope (Std. Error) ^a	p-Value	
			Low	Medium	High			
c) Minimal (R ² =0.010)	≤18.6	1982	269.96 (68)	281.77 (125)	280.53 (51)	0.491 (2.656)	0.257 ^b 0.853 ^c	
		1985	267.38 (66)	273.20 (122)	270.50 (50)			
		1987	252.22 (68)	267.42 (125)	266.37 (51)			
	>18.6	1982	266.46 (55)	280.51 (129)	279.89 (73)		-3.399 (2.168)	0.118 ^c
		1985	270.07 (54)	268.78 (127)	276.51 (72)			
		1987	268.18 (55)	267.60 (129)	268.69 (73)			
d) Maximal (R ² =0.003)	≤18.6	1982	266.46 (94)	276.93 (184)	282.33 (79)	-0.591 (1.898)	0.789 ^b 0.756 ^c	
		1985	261.37 (91)	269.86 (179)	274.36 (78)			
		1987	253.78 (94)	262.57 (184)	266.92 (79)			
	>18.6	1982	271.18 (76)	271.38 (172)	284.91 (100)		-1.266 (1.652)	0.444 ^c
		1985	264.81 (75)	266.94 (169)	276.79 (98)			
		1987	255.55 (76)	265.20 (172)	272.12 (100)			

^aSlope and standard error based on difference between 1987 platelet count and 1982 platelet count versus log₂ dioxin.

^bTest of significance for homogeneity of slopes (current dioxin continuous, time categorized).

^cTest of significance for slope equal to 0 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.

Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1982 and 1987 results.

TABLE 13-22. (Continued)

**Longitudinal Analysis of Platelet Count (thousand/cubic mm)
(Continuous)**

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Mean/(n) Examination			Contrast	Difference of Examination Mean Change (95% C.I.)	p-Value
	1982	1985	1987			
Background	265.62 (681)	266.58 (675)	258.12 (681)	All Categories		0.181
Unknown	273.31 (315)	269.68 (309)	261.74 (315)	Unknown vs. Background	-4.07 (-9.88,1.74)	0.170
Low	277.89 (191)	269.12 (188)	265.14 (191)	Low vs. Background	-5.24 (-12.22,1.74)	0.141
High	283.77 (179)	275.71 (176)	269.83 (179)	High vs. Background	-6.44 (-13.60,0.72)	0.078

(R²=0.181)

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

difference in the mean 1982 and 1987 platelet counts for the background and high current dioxin categories was marginally significant with the Ranch Hands in the high category having a greater negative change in mean platelet count than the Comparisons in the background category ($p=0.078$). The differences in the mean platelet counts between 1982 and 1987 for the background, unknown, low, and high current dioxin categories were -7.50, -11.57, -12.75, and -13.94 thousand/ mm^3 .

DISCUSSION

The complete blood count is the most frequently ordered laboratory test in ambulatory medicine. As measures of the three peripheral blood cell lines (erythrocytes, leukocytes, and platelets) the nine variables examined in this chapter are heavily relied upon to indicate disease of the hematopoietic system and, perhaps more often, to alert the clinician to the presence of disease in other organ systems.

In contrast to most organ systems where disease is usually apparent based on the history and physical examination, particular emphasis is placed on the laboratory examination to detect hematologic disorders. MCV, MCH, and MCHC as quantitative indices may provide helpful insight into the proper morphologic classification of anemias.

The total white cell count varies in a broad range of disease states. Though lacking specificity, leukocytosis or leukopenia can serve as a sensitive clue to the presence of a host of infectious, inflammatory, and neoplastic disorders, and can point to the need for further investigation.

As essential elements to normal coagulation, the platelets have a short half-life and are most subject to decreased survival in the presence of a wide range of diseases, toxic chemicals, and numerous prescription and over-the-counter medications. The normal range (130,000/ mm^3 to 400,000/ mm^3) allows subtle changes in platelet survival to occur and not be identified as abnormal. Furthermore, and pertinent to the current study, small differences in the total platelet count do not have a clinically significant effect on clotting mechanisms. In the most recent examination cycle of the Air Force Health Study (AFHS), four participants with serum dioxin assays were found to have platelet counts greater than 500,000/ mm^3 , with the highest count of 580,000/ mm^3 . Detailed chart reviews failed to reveal any common diagnosis in this subgroup of two Ranch Hands and two Comparisons.

There were very few statistically significant associations in reference to the current analyses. In the unadjusted analysis, a slightly higher mean total red cell count was noted in association with the extrapolated initial dioxin level and, for the time since tour of 18.6 years or less, with the current level of serum dioxin as well. Though statistically significant ($p=0.048$ and $p=0.025$, respectively), the differences were not clinically important. There were no apparent differences between the Ranch Hand and Comparison cohorts in the continuous and discrete analyses.

In the analysis of the red cell assessments most commonly employed in medical practice, there was no evidence for any clinically relevant dose-response effect related to the current or extrapolated initial body burden of dioxin. The hemoglobin and hematocrit, for example, tended to increase with dioxin exposure, an effect opposite to that expected if dioxin

had a toxic effect on bone marrow. In addition, Ranch Hand participants with current serum dioxin levels between 15 ppt and 33.3 ppt had a higher incidence of abnormally elevated MCV than those with levels greater than 33.3 ppt (15.9% versus 9.6%).

Of the laboratory variables analyzed, only the total WBC count revealed statistically significant associations consistent with a dose-response effect in all three models, though the direction of the association was opposite to the myelotoxic effect that might be anticipated on the basis of animal and human observational studies cited in the Background section. Under the maximal assumption, an increase in the WBC count was related to the initial dioxin level ($p < 0.001$) and, for those Ranch Hands more removed from service in Vietnam, the current ($p = 0.007$) level of serum dioxin. Those Ranch Hands with high levels of serum dioxin had a significantly higher mean WBC count than Comparisons, though the difference in the means ($6,668/\text{mm}^3$ versus $7,124/\text{mm}^3$) is not clinically significant. These results are consistent with those recently published in the earlier 1987 examination report, which documented a slightly higher, but nonsignificant, mean WBC count in Ranch Hands than Comparisons. Though the discrete analysis revealed no significant differences between the cohorts, the WBC count will bear surveillance in future examination cycles.

A statistically significant association was found between the extrapolated initial (but not the current) level of serum dioxin and platelet count in the unadjusted analysis. As a nonspecific reaction, the platelet count can be elevated in occult inflammatory disease processes and it is tempting to speculate a link between these results and those of the WBC counts described above. Furthermore, by both the continuous and discrete analyses, Ranch Hands in the high current dioxin category had higher mean platelet counts than Comparisons in the background current dioxin category ($p = 0.016$ and $p = 0.050$, respectively). Though the difference in the means between the cohorts cannot be considered clinically significant ($270,050/\text{mm}^3$ versus $259,010/\text{mm}^3$) these results are consistent with a subtle dose-response effect and with those from each of the previous examination cycles.

As in previous examination cycles of the AFHS, three laboratory variables were subjected to longitudinal analysis. No significant differences were found between the Ranch Hand and Comparison cohorts in the MCV, MCH, and platelet count. However, the pattern of decreases in the difference of mean platelet count from the 1982 Baseline examination to the 1987 examination is consistent with a negative dose-response relationship.

In summary, the results of the current analysis reveal no evidence for hematopoietic toxicity secondary to dioxin exposure. Results of several analyses (RBC count, hemoglobin, hematocrit) were statistically significant but were in a direction opposite to that expected. Statistical analyses of two variables (WBC and platelet counts) raise the possibility of subtle biologic effects that cannot be considered clinically significant at this time but that point to the need for followup in future examination cycles. The increased platelet and WBC counts, along with the elevation of erythrocyte sedimentation rates (in the general health assessment) may indicate the presence of a chronic inflammatory response to dioxin exposure.

SUMMARY

The following hematology variables were evaluated for associations with initial dioxin, current dioxin and time, and categorized current dioxin: RBC count, WBC count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, and prothrombin time. All were analyzed as both continuous and discrete variables except MCHC, which was used only as a continuous variable. No participants had an MCHC value outside the SCRF normal range. Tables 13-23, 13-24, and 13-25 summarize the results.

Model 1: Ranch Hands - Log₂ (Initial Dioxin)

RBC count, when used as a continuous variable, exhibited a significant positive association with initial dioxin in the unadjusted maximal analysis ($p=0.048$). Continuous WBC count was also positively associated with initial dioxin under both assumptions in the unadjusted analysis (minimal, $p=0.071$; maximal, $p<0.001$). After adjusting for covariates, however, these associations were not significant.

In the adjusted analysis of WBC count in its continuous form, there was a significant interaction between initial dioxin and race (minimal, $p<0.001$; maximal, $p=0.001$). Under both assumptions, the association with initial dioxin was positive within both race strata, but was greater for Blacks than for non-Blacks.

Both hemoglobin and hematocrit, in their continuous forms, exhibited a marginally significant positive association with initial dioxin in the unadjusted maximal analysis (hemoglobin, $p=0.079$; hematocrit, $p=0.070$). In the adjusted analysis, however, the associations were not significant.

In the continuous minimal analysis of MCV, there was a significant interaction between initial dioxin and lifetime cigarette smoking history ($p=0.045$). The association between initial dioxin and MCV was negative for Ranch Hands who never smoked and was positive for those with a history of cigarette smoking. When MCV was dichotomized, there was a significant interaction between initial dioxin and lifetime cigarette smoking history under both assumptions (minimal, $p=0.019$; maximal, $p=0.014$). Under both assumptions, the risk of an abnormally high MCV was less than 1 for those who never smoked and those with 10 pack-years or less, and was greater than 1 for those with more than 10 pack-years. After this interaction was removed, there was a marginally significant increased risk of an abnormally high MCV under the adjusted maximal analysis ($p=0.087$).

In the adjusted analyses of MCH, a significant interaction between initial dioxin and lifetime cigarette smoking history was present under the minimal assumption when MCH was continuous ($p=0.015$) and under the maximal assumption when MCH was dichotomized ($p=0.016$). For the continuous evaluation, the association with initial dioxin was negative for those who never smoked and was positive for those with a history of cigarette smoking. For the discrete variable, those with no smoking history and those with 10 pack-years or less had risks of an abnormally high MCH that were less than 1, and those with more than 10 pack-years had a risk that was greater than 1.

In the analyses of MCV and MCH, in both discrete and continuous forms, significant interactions occurred between initial dioxin and lifetime cigarette smoking history. In general,

TABLE 13-23.

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

Variable	Unadjusted		Adjusted	
	Minimal	Maximal	Minimal	Maximal
Laboratory				
Red Blood Cell Count ^a (C)	NS	+0.048	NS	NS
Red Blood Cell Count (D)	NS	NS	NS	NS
White Blood Cell Count ^a (C)	NS*	+<0.001	****	****
White Blood Cell Count (D)	NS	NS	NS	NS
Hemoglobin ^a (C)	NS	NS*	NS	NS
Hemoglobin (D)	NS	NS	NS	NS
Hematocrit ^a (C)	NS	NS*	NS	NS
Hematocrit (D)	ns	NS	NS	NS
Mean Corpuscular Volume ^a (C)	NS	ns	** (NS)	NS
Mean Corpuscular Volume (D)	NS	NS	** (NS)	** (NS*)
Mean Corpuscular Hemoglobin ^a (C)	NS	ns	** (NS)	ns
Mean Corpuscular Hemoglobin (D)	NS	NS	NS	** (NS)
Mean Corpuscular Hemoglobin Concentration ^a (C)	NS	ns	** (ns)	ns
Platelet Count ^a (C)	NS	+0.030	NS	NS
Platelet Count (D)	NS	NS	NS	NS
Prothrombin Time ^a (C)	NS	NS	** (+0.041)	NS
Prothrombin Time (D)	NS	ns	NS	NS

^aSlope in either direction considered adverse for this variable.

C: Continuous analysis.

D: Discrete analysis.

+: Slope nonnegative for continuous analysis.

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

NS*: Marginally significant ($0.05 < p \leq 0.10$).

** (NS)/** (ns): Log_2 (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.

** (NS*): Log_2 (initial dioxin)-by-covariate interaction ($0.01 < p \leq 0.05$); marginally significant when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.

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

Note: P-value given if $p \leq 0.05$.

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis; a capital "NS" for white blood cell count (discrete) and hemoglobin (discrete) does not imply directionality due to log-linear analysis.

TABLE 13-24.
Summary of Current Dioxin and Time Analyses for Hematology
Variables Based on Minimal and Maximal Assumptions
(Ranch Hands Only)

Variable	Minimal			Unadjusted			Maximal		
	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Laboratory									
Red Blood Cell Count ^a (C)	NS	NS	NS	ns	+0.025	NS			
Red Blood Cell Count (D)	NS*	ns	NS	+0.012	ns	NS*			
White Blood Cell Count ^a (C)	NS	NS	NS*	NS	NS*	+0.007			
White Blood Cell Count (D)	NS	NS	NS	NS	NS	NS			
Hemoglobin ^a (C)	ns	NS	NS	-0.036	+0.010	ns			
Hemoglobin (D)	NS	NS	NS	0.006	0.012	NS			
Hematocrit ^a (C)	ns	NS	NS	ns*	+0.018	ns			
Hematocrit (D)	NS	ns	ns	NS	ns	NS			
Mean Corpuscular Volume ^a (C)	ns	NS	ns	ns	ns	ns			
Mean Corpuscular Volume (D)	NS	ns	ns	ns	NS	NS			
Mean Corpuscular Hemoglobin ^a (C)	ns	NS	ns	ns	NS	ns			
Mean Corpuscular Hemoglobin (D)	ns	NS	ns	ns	NS	NS			
Mean Corpuscular Hemoglobin Concentration ^a (C)	ns	NS	NS	ns	NS	ns			
Platelet Count ^a (C)	ns	NS	NS	ns	NS	NS			
Platelet Count (D)	NS	ns	NS	NS	NS	NS			
Prothrombin Time ^a (C)	ns	NS	NS	NS	NS	NS			
Prothrombin Time (D)	ns	NS	ns	ns	NS	ns			

^aSlope in either direction considered adverse for this variable.

C: Continuous analysis.

D: Discrete analysis.

+: C*T: Relative risk for ≤18.6 category less than relative risk for >18.6 category.

≤18.6 and >18.6: Slope nonnegative for continuous analysis.

-.: C*T: Slope for ≤18.6 category greater than slope for >18.6 category.

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

NS*/ns*: Marginally significant ($0.05 < p \leq 0.10$).

Note: P-value given if $p \leq 0.05$.

C*T: Log₂ (current dioxin)-by-time interaction hypothesis test.

≤18.6: Log₂ (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.

>18.6: Log₂ (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.

A capital "NS" denotes relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category, relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk/slope for ≤18.6 category greater than relative risk/slope for >18.6 category, relative risk less than 1.00 for discrete analysis, or slope negative for continuous analysis; a capital "NS" for white blood cell count (discrete) and hemoglobin (discrete) does not imply directionality due to log-linear analysis.

TABLE 13-24. (Continued)
Summary of Current Dioxin and Time Analyses for Hematology
Variables Based on Minimal and Maximal Assumptions
(Ranch Hands Only)

Variable	Adjusted					
	C*T	Minimal		Maximal		
		≤18.6	>18.6	C*T	≤18.6	>18.6
Laboratory						
Red Blood Cell Count ^a (C)	NS	NS	NS	** (ns)	** (NS*)	** (NS)
Red Blood Cell Count (D)	NS*	ns	NS	+0.011	ns	+0.018
White Blood Cell Count ^a (C)	** (NS)	** (ns)	** (NS*)	** (NS)	** (NS)	** (<0.001)
White Blood Cell Count (D)	NS	NS	NS	NS	NS	NS
Hemoglobin ^a (C)	NS	NS	NS	ns*	+0.024	ns
Hemoglobin (D)	NS	NS	NS	0.043	NS	NS
Hematocrit ^a (C)	NS	NS	NS	ns	+0.037	ns
Hematocrit (D)	NS	ns	ns	NS	ns	NS
Mean Corpuscular Volume ^a (C)	ns	NS	NS	ns	NS	ns
Mean Corpuscular Volume (D)	ns	NS	NS	ns	NS	NS
Mean Corpuscular Hemoglobin ^a (C)	ns	NS	NS	ns	NS	ns
Mean Corpuscular Hemoglobin (D)	ns	NS	ns	ns	NS	NS
Mean Corpuscular Hemoglobin Concentration ^a (C)	NS	ns	ns	ns	NS	ns
Platelet Count ^a (C)	ns	NS	ns	NS	NS	NS
Platelet Count (D)	NS	ns	NS	NS	NS	NS
Prothrombin Time ^a (C)	ns	NS	NS	****	****	****
Prothrombin Time (D)	ns*	+0.026	NS	****	****	****

^aSlope in either direction considered adverse for this variable.

C: Continuous analysis.

D: Discrete analysis.

+: C*T: Relative risk for ≤18.6 category less than relative risk for >18.6 category.

≤18.6 and >18.6: Relative risk 1.00 or greater for discrete analysis; slope nonnegative for continuous analysis.

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

NS*/ns*: Marginally significant ($0.05 < p \leq 0.10$).

** (NS)/** (ns): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.

** (NS*): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01 < p \leq 0.05$); marginally significant when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.

** (<0.001): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01 < p \leq 0.05$); significant ($p < 0.001$) when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.

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

Note: P-value given if $p \leq 0.05$.

C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.

≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.

>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.

A capital "NS" denotes relative risk/slope for ≤18.6 category less than relative risk/slope for >18.6 category, relative risk 1.00 or greater for discrete analysis, or slope nonnegative for continuous analysis; a lowercase "ns" denotes relative risk/slope for ≤18.6 category greater than relative risk/slope for >18.6 category, relative risk less than 1.00 for discrete analysis, or slope negative for continuous analysis; a capital "NS" for white blood cell count (discrete) and hemoglobin (discrete) does not imply directionality due to log-linear analysis.

TABLE 13-25.

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

Variable	All	Unadjusted		
		Unknown versus Background	Low versus Background	High versus Background
Laboratory				
Red Blood Cell Count ^a (C)	NS	ns*	ns	NS
Red Blood Cell Count (D)	NS	ns	ns	ns
White Blood Cell Count ^a (C)	0.017	NS	NS*	+0.005
White Blood Cell Count ^b (D)	NS	ns	ns*	ns
White Blood Cell Count ^c (D)		ns	ns	ns
Hemoglobin ^a (C)	NS	NS	NS	NS*
Hemoglobin ^b (D)	NS	ns	NS	ns
Hemoglobin ^c (D)		ns	NS	ns
Hematocrit ^a (C)	NS	ns	NS	NS
Hematocrit (D)	NS	ns	NS	ns
Mean Corpuscular Volume ^a (C)	NS	NS*	NS	NS
Mean Corpuscular Volume (D)	NS*	ns	+0.017	ns
Mean Corpuscular Hemoglobin ^a (C)	NS*	+0.012	NS	NS
Mean Corpuscular Hemoglobin (D)	NS	NS	NS	NS
Mean Corpuscular Hemoglobin Concentration ^a (C)	0.022	+0.007	+0.031	NS
Platelet Count ^a (C)	NS*	NS	NS	+0.016
Platelet Count (D)	NS	NS	NS	+0.050
Prothrombin Time ^a (C)	NS	ns	ns	NS
Prothrombin Time (D)	NS	ns	ns*	ns

^aDifference in either direction considered adverse for this variable.

^bLow contrasted with normal for the last three columns.

^cHigh contrasted with normal for the last three columns.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.

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

NS*/ns*: Marginally significant ($0.05 < p \leq 0.10$).

Note: P-value given if $p \leq 0.05$.

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

TABLE 13-25. (Continued)

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

Variable	All	Adjusted		
		Unknown versus Background	Low versus Background	High versus Background
Laboratory				
Red Blood Cell Count ^a (C)	NS	ns	ns	NS
Red Blood Cell Count (D)	NS	ns	ns	NS
White Blood Cell Count ^a (C)	0.010	ns	NS	+0.004
White Blood Cell Count ^b (D)	NS	ns	ns	ns
White Blood Cell Count ^c (D)		ns	ns	ns*
Hemoglobin ^a (C)	NS	ns	NS	NS
Hemoglobin ^b (D)	NS	ns	NS	ns
Hemoglobin ^c (D)		ns	NS	ns
Hematocrit ^a (C)	** (NS)	** (ns)	** (NS)	** (NS)
Hematocrit (D)	NS	ns	NS	ns
Mean Corpuscular Volume ^a (C)	NS	NS	NS	NS
Mean Corpuscular Volume (D)	0.034	ns	+0.017	NS
Mean Corpuscular Hemoglobin ^a (C)	NS	NS*	NS	NS
Mean Corpuscular Hemoglobin (D)	NS	ns	NS	NS
Mean Corpuscular Hemoglobin Concentration ^a (C)	0.029	+0.016	+0.024	NS
Platelet Count ^a (C)	** (NS)	** (NS)	** (NS)	** (NS*)
Platelet Count (D)	NS	NS	NS	+0.050
Prothrombin Time ^a (C)	****	****	****	****
Prothrombin Time (D)	****	****	****	****

^aDifference in either direction considered adverse for this variable.

^bLow contrasted with normal for the last three columns.

^cHigh contrasted with normal for the last three columns.

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk 1.00 or greater for discrete analysis; difference in means nonnegative for continuous analysis.

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

NS*/ns*: Marginally significant ($0.05 < p \leq 0.10$).

** (NS)/** (ns): Categorized current dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); not significant when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.

** (NS*): Categorized current dioxin-by-covariate interaction ($0.01 < p \leq 0.05$); marginally significant when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.

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

Note: P-value given if $p \leq 0.05$.

A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

the association with initial dioxin increased with an increased cigarette smoking history. The association with initial dioxin was negative but nonsignificant for nonsmokers (0 pack-years) and positive but nonsignificant for Ranch Hands with more than 10 pack-years. For Ranch Hands with 10 or fewer pack-years, the association with initial dioxin was also nonsignificant.

In the minimal analysis of MCHC there was a significant interaction between initial dioxin and age ($p=0.025$). For the younger Ranch Hands, the association with initial dioxin was negative. For the older Ranch Hands the association was positive. Without this interaction, the association between MCHC and initial dioxin was nonsignificant. Under the unadjusted maximal analysis, platelet count, in its continuous form, exhibited a significantly positive association with initial dioxin ($p=0.030$).

In the continuous analysis of prothrombin time, there was a significant interaction between initial dioxin and lifetime cigarette smoking history under the minimal analysis ($p=0.011$). The association between prothrombin time and initial dioxin was significant only for those Ranch Hands who had 10 pack-years or less ($p=0.001$). When this interaction was removed from the model, a significant positive association was exhibited between prothrombin time and initial dioxin ($p=0.041$).

The longitudinal analyses of MCV, MCH, and platelet count displayed no significant associations with initial dioxin.

Model 2: Ranch Hands - Log₂ (Current Dioxin) and Time

Under the unadjusted discrete analysis of RBC count, the association with current dioxin showed a significant or marginally significant difference between the time since tour strata under both assumptions (minimal, $p=0.066$; maximal, $p=0.012$). For time less than or equal to 18.6 years, the relative risks were less than 1, and for time greater than 18.6 years, the relative risks were greater than 1. However, the only risk that was even marginally significant was under the maximal assumption when time was greater than 18.6 years ($p=0.062$).

When RBC count was analyzed in continuous form unadjusted for any covariates, there was a significant positive association with current dioxin when time was no more than 18.6 years, under the maximal assumption ($p=0.025$). When time was more than 18.6 years, there was also a positive association unadjusted for covariates between WBC count in its continuous form and current dioxin that was marginally significant under the minimal assumption ($p=0.090$) and was significant under the maximal assumption ($p=0.007$). This association was also marginally significant under the maximal assumption when time was no more than 18.6 years ($p=0.059$).

The association between hemoglobin in its continuous form and current dioxin was significantly different between the time strata under the maximal assumption based on the unadjusted analysis ($p=0.036$). This association was significantly positive for time no more than 18.6 years ($p=0.010$), and was negative, but nonsignificant, for time greater than 18.6 years. The same trend was found in the maximal analysis of hematocrit, but the interaction between current dioxin and time was only marginally significant ($p=0.063$). There was also a

significant current dioxin-by-time interaction in the maximal analysis of hemoglobin in its discrete form ($p=0.006$). The overall test of independence between hemoglobin and the current dioxin categories was significant for time no more than 18.6 years ($p=0.012$), and was nonsignificant for time greater than 18.6 years.

In the adjusted maximal continuous analysis of RBC count, there was a significant interaction between current dioxin, time, and age ($p=0.038$). For the younger Ranch Hands, the current dioxin-by-time interaction was not significant, but for the older Ranch Hands, it was significant ($p=0.035$). The association between RBC count and current dioxin was positive when time was no more than 18.6 years and was significantly negative for time greater than 18.6 years ($p=0.033$) for the older Ranch Hands. When RBC count was analyzed in discrete form, the adjusted results were similar to the unadjusted analysis.

In the adjusted analysis of WBC count in its continuous form, there was a significant interaction between current dioxin, time, and age under the minimal assumption ($p=0.021$) and between current dioxin, time, and race under the maximal assumption ($p=0.050$). For Ranch Hands born in or after 1942, in the minimal cohort, the current dioxin-by-time interaction was significant ($p=0.025$) with the association being negative for the more recent (≤ 18.6 years) time stratum and positive for the less recent (>18.6 years) time stratum. For Black Ranch Hands, in the maximal cohort, the current dioxin-by-time interaction was marginally significant ($p=0.080$) with the association being significantly positive for the less recent time stratum. For non-Blacks, the current dioxin-by-time interaction was not significant. However, for time over 18.6 years, there was a positive association between WBC count and current dioxin ($p<0.001$). When the interactions were removed, there was a positive association between WBC count and current dioxin for time greater than 18.6 years (minimal, $p=0.059$; maximal, $p<0.001$).

In the maximal adjusted continuous analysis of hemoglobin there was a significant positive association with current dioxin when time did not exceed 18.6 years ($p=0.024$). This was marginally different from the negative association when time was greater than 18.6 years. There was also a significant positive association between hematocrit in its continuous form and current dioxin when time did not exceed 18.6 years ($p=0.037$). In the discrete analysis of hemoglobin, the overall test of independence between hemoglobin and the current dioxin categories was significant under the maximal assumption ($p=0.043$).

Under the maximal analysis of prothrombin time in continuous form, a significant interaction among current dioxin, time since tour, and current cigarette smoking was present ($p=0.006$). However, the current dioxin-by-time since tour interaction was not significant within any of the four current cigarette smoking strata. When prothrombin time was dichotomized, there was a significant interaction amount current dioxin, time since tour, and race under the maximal assumption ($p=0.006$). Under the minimal assumption, the current dioxin-by-time since tour interaction was marginally significant ($p=0.089$), and the association between current dioxin and prothrombin time was significantly positive for time since tour of 18.6 years or less ($p=0.026$).

In the longitudinal analyses of MCV, MCH, and platelet count, the current dioxin-by-time since tour interactions were nonsignificant. However, a marginally significant ($p=0.082$)

positive association between current dioxin and the change in MCV from 1982 to 1987 was detected for Ranch Hands in the minimal cohort with 18.6 years or less since tour.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The WBC count means, in the unadjusted analysis, differed significantly among the current dioxin categories ($p=0.017$). The means in the categories that consisted of Ranch Hands were all greater than the mean in the Comparisons' category. The differences were marginally significant for the low versus background contrast ($p=0.072$) and significant for the high versus background contrast ($p=0.005$).

The unadjusted mean RBC count in the unknown current dioxin category was marginally less than the mean in the background category ($p=0.088$). In contrast, the unadjusted MCV mean in the unknown current dioxin category was marginally greater than the mean in the background category ($p=0.057$). When MCV was discrete, the percentages of abnormally high values differed marginally among the categories ($p=0.070$). This was due to the fact that the percentage of abnormalities in the low category was significantly greater than the percentage in the background category ($p=0.017$). In the unadjusted analysis of hemoglobin, the mean in the high current dioxin category was marginally greater than the mean in the background category ($p=0.090$).

The unadjusted MCH means were marginally different among the current dioxin categories ($p=0.072$), with the unknown category having a significantly higher mean than the background category ($p=0.012$). The overall contrast was also marginally significant in the analysis of platelet count ($p=0.083$) and was significant in the analysis of MCHC ($p=0.022$). In both of these analyses, the means in the unknown, low, and high categories exceeded the mean in the background category. The unadjusted analysis of MCHC revealed a significantly greater mean in the unknown category than in the background category ($p=0.007$) and a significantly greater mean in the low category than in the background category ($p=0.031$).

In the unadjusted discrete analysis of prothrombin time, the percentage of abnormalities in the background category was marginally greater than the percentage in the low category ($p=0.057$).

In the adjusted analyses of the continuous variables, only WBC count and MCHC had significant overall contrasts (WBC: $p=0.010$; MCHC: $p=0.029$). In the WBC count analysis, the mean in the high category was significantly greater than the mean in the background category ($p=0.004$). In the analysis of MCHC, the unknown and low categories significantly exceeded the background category (unknown versus background: $p=0.016$; low versus background: $p=0.024$).

An interaction between categorized current dioxin and age was present in the continuous analyses of hematocrit ($p=0.025$) and platelet count ($p=0.031$). In the stratum consisting of participants born in or after 1942, the overall contrast was marginally significant for the hematocrit analysis ($p=0.091$), and was significant for the platelet count analysis ($p=0.010$). Overall contrast results from the stratum containing older participants were nonsignificant in the analyses of these two variables. After the interaction was eliminated from the analysis of platelet count, there was a marginally significant difference between the

high and background categories ($p=0.057$). There was also a marginally significant difference between the unknown and background categories in the analysis of MCH ($p=0.090$).

In the adjusted analyses of the discrete form of the hematology variables, the only significant overall contrast was in the analysis of MCV ($p=0.034$). Within this analysis, the percentage of abnormalities was significantly greater in the low category than in the background category ($p=0.017$). In the discrete analysis of platelet count, there was a significant difference in the percentages of abnormalities between the high and background categories ($p=0.050$). The Ranch Hands in the high category had a greater percentage of abnormally high platelet counts than the Comparisons in the background category.

In the adjusted analysis of prothrombin time in continuous form, there was a significant interaction between categorized current dioxin and age ($p=0.004$). For the younger participants there was a significant difference among the current dioxin categories ($p=0.045$) with the mean in the low category significantly less than the mean in the background category ($p=0.046$). For the older participants, the overall difference among the categories was marginally significant ($p=0.082$) with the adjusted mean in the unknown category marginally less than the adjusted mean in the background category ($p=0.100$). In the adjusted discrete analysis of prothrombin time, there was a significant interaction between categorized current dioxin and age ($p=0.005$) and between categorized current dioxin and current cigarette smoking ($p=0.028$). The overall contrast of the four current dioxin categories was significant for the younger participants who never smoked ($p=0.041$) and was marginally significant for the older participants who currently smoke ($p=0.093$).

The overall contrast of the current dioxin categories was nonsignificant for the longitudinal analyses of MCV, MCH, and platelet count. The change in the mean platelet count between 1982 and 1987 was greater for Ranch Hands in the high category than for the Comparisons in the background category ($p=0.078$).

CONCLUSION

Several variables showed an association with initial dioxin in the unadjusted model, but when the model was adjusted for covariates, the association became nonsignificant. Only four hematology variables had a significant, or marginally significant, current dioxin-by-time since tour interaction. For hemoglobin and hematocrit, this interaction only occurred under the maximal assumption, where the association with current dioxin was positive when time was no more than 18.6 years and negative when time was greater than 18.6 years. For the discrete RBC count analysis, the risk of an abnormally low count was less than 1 when time did not exceed 18.6 years and was greater than 1 when time was more than 18.6 years. From these risks, a greater percentage of abnormals would be expected in the low dioxin category when time was no more than 18.6 years, and a higher percentage of abnormals would be expected in the high dioxin category when time was more than 18.6 years. Since a low RBC count was considered abnormal for the purpose of these statistical analyses, the trend in relation to current dioxin was similar to that in the continuous analyses of hemoglobin and hematocrit. In the discrete analysis of prothrombin time, the risk of an abnormally high prothrombin time was greater when time since tour did not exceed 18.6 years than when time was greater than 18.6 years. Thus, the trend in relation to current dioxin also was similar to that in the continuous analyses of hemoglobin and hematocrit. In the categorized current dioxin analyses, whenever the overall contrast showed significant, or marginally significant,

differences among the categories, the mean level or percent abnormal in the three categories of Ranch Hands tended to exceed the corresponding mean level or percent abnormal in the background category that consisted of Comparisons.

The longitudinal analyses of MCV, MCH, and platelet count displayed no significant associations with dioxin.

In summary, the results of the current analysis reveal no evidence for hematopoietic toxicity secondary to dioxin exposure. Statistical analyses of two variables (WBC and platelet counts) raise the possibility of subtle biologic effects that cannot be considered clinically significant at this time but that can point to the need for followup in future examination cycles. The increased platelet and WBC counts, along with the elevation of erythrocyte sedimentation rates (in the general health assessment) may indicate the presence of a chronic inflammatory response to dioxin exposure.

CHAPTER 13

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