TABLE 13-22. (Continued)

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

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Mean/(n) Current Dioxin Low	Medium	High	Slope (Std. Error)[a]	p-Value
c) Minimal							0.257[b]
(R^2=0.010)	≤18.6	1982	269.96 (68)	281.77 (125)	280.53 (51)	0.491 (2.656)	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							0.789[b]
(R^2=0.003)	≤18.6	1982	266.46 (94)	276.93 (184)	282.33 (79)	-0.591 (1.898)	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)		

[a]Slope and standard error based on difference between 1987 platelet count and 1982 platelet count versus log_2 dioxin.

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

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

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
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 1982	1985	1987	Contrast	Difference of Examination Mean Change (95% C.I.)	p-Value
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
	(R^2=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/mm^3 versus 7,124/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/mm^3 versus 259,010/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 - Log_2 (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

[a]Slope 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 ($0.05<p\leq0.10$).
** (NS)/** (ns): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.
**(NS*): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); marginally significant when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.
****: Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); refer to Appendix Table L-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or 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)

	Unadjusted					
	Minimal			Maximal		
Variable	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

[a]Slope 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 ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour 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 13-24. (Continued)

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

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
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	****	****	****

[a]Slope 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 ($0.05<p\leq0.10$).

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

** (NS*): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); 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 ($0.01<p\leq0.05$); 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 ($p\leq0.01$); refer to Appendix Table L-1 for a detailed description of this interaction.

Note: P-value given if $p\leq0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour 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	Unadjusted: Low versus Background	Unadjusted: 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

[a]Difference in either direction considered adverse for this variable.

[b]Low contrasted with normal for the last three columns.

[c]High 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 ($0.05<p\leq0.10$).

Note: P-value given if $p\leq0.05$.

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

TABLE 13-25. (Continued)

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

Variable	All	Adjusted: Unknown versus Background	Adjusted: Low versus Background	Adjusted: 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)	****	****	****	****

[a]Difference in either direction considered adverse for this variable.
[b]Low contrasted with normal for the last three columns.
[c]High 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 ($0.05<p\leq0.10$).
** (NS)/** (ns): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table L-1 for a detailed description of this interaction.
** (NS*): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); 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 ($p\leq0.01$); refer to Appendix Table L-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater for discrete analysis or difference of means nonnegative for continuous analysis; a lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis; a capital "NS" in the first column does not imply directionality.

the association with initial dioxin increased with an increased cigarette smoking history. The association with initial dioxin was negative but nonsigificant 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 - Log_2 (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 ($\leq$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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