CHAPTER 16

HEMATOLOGICAL EVALUATION

INTRODUCTION

Although direct impairment of the hematopoietic system may result from exposure to chlorophenols or dioxin, marked abnormalities in many of the circulating hematological elements may also be due to the severe and often endstage toxicity observed in other organs or organ systems. Animal experiments have confirmed both direct and indirect hematopoietic effects of TCDD. In a chronic low-dose feeding study of TCDD in eight monkeys, decreased hemoglobin and hematocrit values were noted at the 6-month mark in all animals.[1] Four of these monkeys expired in 7 to 11 months and all had anemia, leukopenia, and thrombocytopenia. Necropsy of three sacrificed animals at 1 year showed multi-organ pathology including bone marrow degeneration, atrophy of lymphopoietic tissue, and numerous hemorrhages in a variety of organs. In another monkey experiment, using single low and high doses of TCDD, early hematological effects included increased neutrophil counts in the low-dose group and lymphopenia and thrombocytopenia in the high-dose group.[2] At the end of the experiment, half the sternal bone-marrow samples revealed a decrease in overall cellularity and an increase in the myeloid-erythroid cell ratio.

Rat experiments with TCDD demonstrated relatively consistent results. One study revealed elevated erythrocyte, reticulocyte, and neutrophil counts with depressed values for the mean corpuscular volume, mean corpuscular hemoglobin, platelet counts, and clot retraction times.[3] The authors attributed most of these effects to terminal dehydration and nonspecific toxicity. Another rat study using gavage doses of TCDD varying from 0.001 to 1.0 µg/kg demonstrated depressed red blood cell counts and packed cell volumes in the high-dose group.[4] In a mixed-dose regimen using rats, mice, and guinea pigs, dose-related decreases in lymphocyte and leukocyte numbers were observed in mice and guinea pigs within 1 week following TCDD administration.[5] Thrombocytopenia and hemoconcentration were found in rats. Because of the lymphopenia in mice and guinea pigs, TCDD was judged to be immunosuppressive.

In general, human observational studies showed fewer and less consistent hematological 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.[6] In two industrial accidents involving significant contamination with TCDD and resulting cases of chloracne, only temporary depression of peripheral leukocyte and lymphocyte formation was observed.[7,8]

Two contemporary indepth morbidity studies[9,10] of the Nitro, West Virginia, accident included routine clinical complete blood counts and differential counts, and hemoglobin and hematocrit determinations. Though these studies shared overlapping study cohorts, they did not report any of the

hematological results in their publications; presumably, there were no significant differences in any of the parameters between the exposed and the unexposed cohorts.

The two pilot studies of TCDD-contaminated residential areas in Missouri also included routine hematological assays of peripheral blood.[11,12] One study paradoxically noted a significantly increased mean platelet count in the high-risk group, although the data were not adjusted for smoking.[11] The Quail Run study, predominantly emphasizing cell-mediated immunity, found significant group differences in the mean leukocyte count, mean absolute granulocyte count, and the mean percentage of monocytes in the differential count.[12] Unfortunately, the authors neglected to identify the group (exposed or unexposed) that had the abnormal hematological findings. However, the finding of a significantly higher proportion of individuals with white blood cell counts exceeding 10,000/mm^3 was in the exposed group.

Baseline Summary Results

A number of statistically significant group differences and interactions emerged in the analysis of the 1982 Baseline examination. The Ranch Hand group had a significantly higher adjusted mean red blood cell corpuscular volume and corpuscular hemoglobin value than the Comparison group ($p=0.05$, $p=0.04$, respectively), although the magnitude of the difference was small in each case. The Ranch Hand adjusted mean values for six other parameters, i.e., red blood cell count, white blood cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin concentration, and platelet count, were nearly identical to the adjusted means of the Comparison group, and all were well within normal range. Similarly, the percent of abnormal values for these eight variables, as established by the upper and lower limits of normal, did not vary by group.

Linear models demonstrated the profound effect of smoking, as measured in pack-years. With increased smoking, white blood cell, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and platelet values increased, whereas the mean corpuscular hemoglobin concentration showed a significant negative association with smoking. The red blood cell count revealed a borderline significant negative relationship to smoking. No statistically significant group-by-smoking interactions were detected.

The exposure index analyses conducted within the Ranch Hand group disclosed two statistically significant exposure-level effects as well as seven significant or borderline-significant exposure-level-by-smoking interactions. In the officer cohort, the percentage of mean corpuscular hemoglobin abnormalities increased with increasing exposure level. The high-exposure group also had the highest percentage of mean corpuscular hemoglobin concentration abnormalities. No significant associations were found, however, in the enlisted flyer or enlisted groundcrew cohort. Five interactions involved a decreasing association (gradient of slopes) between the hematological measure and pack-years of smoking with increasing exposure level, one showed an increasing association with increasing exposure level, and one was uninterpretable. The report concluded that the overall statistical findings were somewhat consistent among themselves, and that medical morbidity was not significant.

Parameters of the 1985 Hematological Evaluation

The 1985 hematological assessment was identical to the 1982 Baseline evaluation. The eight hematological variables were red blood cell count (RBC), white blood cell count (WBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count (PLT); these variables were determined by routine hematological procedures. The normal ranges of the SCRF-determined values differed somewhat from those employed in 1982 by the Kelsey-Seybold Clinic.

As before, the analysis of the hematological data included the covariates of age, race, occupation, and smoking. Updated and more comprehensive smoking data, in terms of pack-years and current smoking (including cigar- and pipe-smoking), were used in most analyses.

Excluded were three individuals with fever at the time of examination (two Ranch Hands and one Comparison). Hematological variables in the continuous form were analyzed by general linear models adjusting for age, race, occupation, and smoking. The hematological data, trichotomized as abnormally low, normal, or abnormally high, were subjected to log-linear (logit) analysis, adjusted for the same covariates. Minor differences in the table totals within this chapter reflect rare missing data for either the dependent variables or the covariates. Parallel analyses using Original Comparisons can be found in Tables N-4 through N-9 of Appendix N.

RESULTS AND DISCUSSION

General

Eight hematological assays were performed on peripheral blood specimens obtained from all participants on the first day of the physical examination. Table 16-1 lists the assays, the abbreviations used in this chapter, the SCRF laboratory normal range for each assay, and the required laboratory coefficient of variation for each assay. The SCRF laboratory norms varied to some extent from the values used at the Baseline examination (see pages XVI-3-1, Baseline Report). The SCRF laboratory coefficients of variation met or exceeded contract requirements and were uniformly achieved due to the precision of the Coulter 5-Plus automated instrument, in conjunction with rigorous FIR CUSUM quality control techniques (see Chapter 6).

The overall precision in the laboratory aspects of the hematological assays is reflected in the analytic ability to discern minute mean shifts between groups. Representative statistical power statements are as follows. Sample sizes were sufficiently large to detect a 0.87 percent mean shift in RBC and a 2.5 percent mean shift in PLT values using an α-level of 0.05 (two-sided) and a power of 0.80. Further, the sample sizes were sufficient to detect a 1.66-fold increase in the frequency of abnormal values for RBC, and a 1.96-fold increase in the frequency of abnormal values for PLT, with 80 percent certainty.

TABLE 16-1.

Laboratory Parameters for
Hematological Test Variables

Hematological Test	Abbreviation	SCRF Laboratory Normal Range	Contract Required Coefficient of Variation (in percent)
Red Blood Cell Count	RBC	4.3-5.9 million/cubic mm	2.0
White Blood Cell Count	WBC	4.5-11.0 thousand/cubic mm	2.5
Hemoglobin	HGB	13.9-16.3 grams/100 ml	1.1
Hematocrit	HCT	39.0-55.0 ml/100 ml	3.0
Mean Corpuscular Volume	MCV	80.0-97.0 cubic micra	2.0
Mean Corpuscular Hemoglobin	MCH	26.0-34.0 micromicrogram	2.0
Mean Corpuscular Hemoglobin Concentration	MCHC	31.0-37.0 percent	2.0
Platelet Count	PLT	130-400 thousand/cubic mm	3.5

The statistical analyses in this chapter are presented in the following order: unadjusted tests, covariate tests of association, adjusted analyses, exposure analyses, and longitudinal contrasts. A variable-by-variable discussion summarizes all of the analyses, and representative exposure analyses are also presented. Group-by-covariate interactions are narratively presented, and illustrated by calculating Ranch Hand-Comparison differences at selected covariate levels. The interaction data tables are found in Tables N-2 and N-3 of Appendix N.

Unadjusted Categorical Analyses

Data from the eight hematological variables were categorized as abnormally low, normal, or abnormally high according to the SCRF laboratory norms cited in Table 16-1. The frequency distribution of these discretized data is presented by group in Table 16-2. As shown, there were no statistically significant, or even marginally significant, differences between the groups. Only one abnormal MCHC value was found among all study participants.

TABLE 16-2.

Unadjusted Categorical Analyses for Hematological Variables by Group

Variable	Group	Abnormally Low Number	Abnormally Low Percent	Normal Number	Normal Percent	Abnormally High Number	Abnormally High Percent	Total	p-Value*
RBC	Ranch Hand	30	3.0	976	96.2	8	0.8	1,014	0.910
	Comparison	42	3.2	1,239	95.9	11	0.8	1,292	
WBC	Ranch Hand	45	4.4	906	89.4	62	6.1	1,013	0.883
	Comparison	63	4.9	1,149	88.9	80	6.2	1,292	
HGB	Ranch Hand	39	3.8	752	74.2	223	22.0	1,014	0.848
	Comparison	44	3.4	960	74.3	288	22.3	1,292	
HCT	Ranch Hand	11	1.1	1,001	98.7	2	0.2	1,014	0.999
	Comparison	15	1.2	1,274	98.6	3	0.2	1,292	
MCV	Ranch Hand	10	1.0	857	84.5	147	14.5	1,014	0.992
	Comparison	13	1.0	1,094	84.7	185	14.3	1,292	
MCH	Ranch Hand	7	0.7	943	93.0	64	6.3	1,014	0.755
	Comparison	7	0.5	1,211	93.7	74	5.7	1,292	
MCHC	Ranch Hand	1	0.1	1,013	99.9	0	0.0	1,014	--
	Comparison	0	0.0	1,292	100.0	0	0.0	1,292	
PLT	Ranch Hand	5	0.5	987	97.4	21	2.1	1,013	0.828
	Comparison	3	0.2	1,264	97.9	24	1.9	1,291	

*Chi-square test, 2 d.f., except for HCT and PLT which were obtained from continuity adjusted chi-square tests on 1 d.f. (Abnormally high category pooled with normal, and abnormally low category pooled with normal for HCT and PLT, respectively.)

--Only one abnormal MCHC value; p-value not given.

Unadjusted Analyses of Continuous Data

The unadjusted tests of group means from the continuous data for the eight variables are displayed in Table 16-3. The variables WBC and PLT were analyzed in logarithmic units because of their right-skewed original distributions. Antilog values of the means are given for ease of interpretation but their standard error or variance terms are consequently omitted since the relevance of these terms pertains only to the logarithmic scale. The sample sizes were 1,014 for the Ranch Hand group and 1,292 for the Comparisons, except for WBC (Ranch Hands, 1,013; Comparisons, 1,292) and PLT (Ranch Hands, 1,013; Comparisons, 1,291). As shown in Table 16-3, there were no statistically significant group differences between the unadjusted means of each variable.

TABLE 16-3.

Unadjusted Continuous Analyses for Hematological Variables (Contrast of Group Means)

Variable	Group Mean±SE		Difference ±SE	t-Statistic	p-Value
	Ranch Hand	Comparison			
RBC	4.964±0.012	4.982±0.010	-0.019±0.016	-1.19	0.233
WBC[a]	7.003	6.891	--	1.34	0.182
HGB	15.624±0.033	15.626±0.029	-0.002±0.044	-0.05	0.958
HCT	45.904±0.097	45.952±0.083	-0.048±0.127	-0.38	0.703
MCV	92.596±0.150	92.346±0.132	0.250±0.200	1.25	0.210
MCH	31.544±0.055	31.431±0.049	0.113±0.074	1.53	0.125
MCHC	34.040±0.021	34.009±0.017	0.031±0.027	1.17	0.243
PLT[a]	265.2	263.0	--	0.96	0.337

[a]Means transformed from log scale.

--Difference and standard errors (SE) not presented, since variables were analyzed on logarithmic scale.

Dependent Variable and Covariate Relationships

The data from the Ranch Hand and Comparison groups were pooled for each of the eight hematological variables and analyzed independently with the covariates of age (born in or after 1942, born before 1942), race (Black, nonblack), occupation (officer, enlisted flyer, enlisted groundcrew), and smoking history (0 pack-years; greater than 0 to 10 pack-years; and greater than 10 pack-years). These analyses are summarized in terms of statistical significance (p-values) in Table 16-4. As noted, each of the dependent variables was substantially affected by one or more of the covariates. The exact nature of the covariate influence, e.g., directionality, significance, consistency across related variables, is presented in the variable-by-variable discussion section. Covariate effects were also analyzed in continuous form with the use of linear regression models (see Table 16-6 and discussion following). In addition, covariate distributions were examined between groups (see Table N-1 of Appendix N).

TABLE 16-4.

Association Between Hematological Variables and Age, Race, Occupation, and Smoking History in the Combined Ranch Hand and Comparison Groups

Variable	Age	Race	Occupation	Smoking History
RBC	0.010	<0.001	NS	NS
WBC	NS*	<0.001	0.001	<0.001
HGB	NS	0.002	<0.001	0.003
HCT	NS	<0.001	NS	NS
MCV	<0.001	<0.001	0.004	<0.001
MCH	<0.001	<0.001	0.003	<0.001
MCHC	--	--	--	--
PLT	NS	NS	NS	0.004

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

NS*: Borderline significant ($0.05<p\leq0.10$).

--Not analyzed due to sparse data.

Adjusted Categorical Analyses

Log-linear (logit) models for each of the hematological variables were fit to adjust for age, race, occupation, and smoking history. In addition, all significant group-by-covariate interactions were examined. The covariate of current level of smoking (used in the adjusted continuous analyses described below) was not included in the categorical analyses to avoid problems with sparse cells. Adjusted relative risks for Ranch Hand-Comparison contrasts were calculated for the categories of abnormally low values versus normal values and for abnormally high values versus normal values. Adjusted relative risks were not computed for the abnormally high versus normal categories for HCT, or for the abnormally low versus normal categories for PLT, due to sparse data. The results of these analyses are given in Table 16-5 and were quite similar to the unadjusted results, with no statistically significant or borderline significant associations found.

TABLE 16-5.

Adjusted Categorical Analyses for Hematological Variables (Abnormal Versus Normal), Adjusted for Age, Race, Occupation, and Smoking

	Abnormally Low vs. Normal		Abnormally High vs. Normal	
Variable	Adj. Relative Risk (95% C.I.)	p-Value	Adj. Relative Risk (95% C.I.)	p-Value
RBC	0.93 (0.59,1.47)	0.762	1.04 (0.48,2.28)	0.920
WBC	0.96 (0.66,1.42)	0.854	0.97 (0.69,1.36)	0.852
HGB	1.12 (0.74,1.80)	0.522	0.98 (0.80,1.19)	0.824
HCT	1.02 (0.51,2.06)[a]	0.954[a]	--	--
MCV	1.08 (0.52,2.26)	0.787	0.99 (0.78,1.26)	0.960
MCH	1.33 (0.56,3.17)	0.525	1.10 (0.79,1.54)	0.574
PLT	--	--	1.14 (0.66,1.98)[b]	0.638[b]

[a] Abnormally low versus normal/abnormally high.

--Not analyzed due to sparse data.

[b] Abnormally high versus normal/abnormally low.

Adjusted Analyses of Continuous Data

General linear regression models were performed, adjusting for age (at the Baseline examination), race, occupation (OCC), smoking history (pack-years [PACKYR]), and current level of smoking (cigarettes per day [CSMOK]). The linear models were fit to examine the main effects of group (GRP) membership, the covariates, and two- and three-factor interactions among these variables (only three-factor interactions involving group were considered). The hierarchical modeling approach as described in Chapter 7, Statistical Methods, was performed to arrive at a "best model" containing the group effect and all statistically significant covariate main effects and interactions.

The results of the adjusted analyses for the hematological variables, along with the significance of the adjusting covariates and covariate interactions are summarized in Table 16-6.

These results indicated a lack of significant group differences for RBC, HGB, HCT, MCV, MCH, and MCHC after adjustment for five covariates. Two analyses, WBC and PLT, showed significant group-by-covariate interactions; the statistics of these interactions (along with borderline interactions for RBC) are given in Table N-2 of Appendix N, and the narrative descriptions of these interactions are included in the following variable-by-variable summary presentations.

Discussion

The following variable-by-variable discussion presents the findings for the unadjusted and adjusted results, main covariate effects, group-associated interactions, and when appropriate, Ranch Hand versus Original Comparison contrasts, and comparisons to Baseline results. The results of the covariate effects and covariate interactions (not involving group) for the adjusted analyses are found in Table 16-6; group-by-covariate interactions are given in Table N-2 of Appendix N.

Red Blood Cell Count (RBC)

Both the categorical and continuous unadjusted analyses found no statistically significant differences in RBC values between groups.

The covariate associations for both groups combined showed a significant effect of age (RBC abnormally low in 4.0% of the older cohort versus 1.9% of the younger; $p=0.010$) and race (Blacks having 6.3% and 4.2% in the abnormally low and high categories versus 2.9% and 0.6% in nonblacks, respectively; $p<0.001$).

Continuous regression analyses also detected significant effects of current smoking ($p=0.004$) and an age-by-occupation interaction ($p=0.013$). The adjusted categorical analysis showed no significant group difference, but the adjusted continuous analysis revealed a borderline significant ($p=0.086$) three-factor interaction of group-by-occupation-by-smoking history. Estimated Ranch Hand-Comparison contrasts revealed a significant difference ($p=0.010$) for enlisted groundcrew, 30 pack-years with Ranch Hands exhibiting a slightly lower RBC count than the Comparisons (see Table N-2 of Appendix N).

TABLE 16-6.

Adjusted Continuous Analyses for Hematological Variables,
(Ranch Hand-Comparison Group Differences)

Variable	Ranch Hand-Comparison Group Difference ± SE	p-Value	Covariate Remarks*
RBC	-0.021±0.015[a]	0.172	AGE*OCC (p=0.013) CSMOK (p=0.004)
WBC	****	****	GRP*RACE*AGE (p=0.005) GRP*AGE*PACKYR (p=0.004) GRP*RACE*OCC (p=0.004)
HGB	-0.034±0.042	0.410	AGE*OCC (p=0.002) RACE*OCC (p=0.013) CSMOK (p<0.001)
HCT	-0.151±0.121	0.210	AGE*OCC (p=0.004) RACE*OCC (p=0.003) OCC*PACKYR (p=0.035) CSMOK (p<0.001)
MCV	0.108±0.188	0.565	RACE*AGE (p<0.001) RACE*OCC (p=0.015) RACE*CSMOK (p=0.025)
MCH	0.062±0.070	0.378	RACE*AGE (p=0.015) CSMOK (p<0.001) OCC (p<0.001)
MCHC	0.032±0.026	0.226	RACE (p=0.001) CSMOK (p=0.042)
PLT	****	****	GRP*RACE*PACKYR (p<0.001) GRP*RACE*CSMOK (p=0.024) OCC (p=0.039) AGE (p=0.006)

*Abbreviations
OCC: Occupation
CSMOK: Current level of smoking (cigarettes per day)
GRP: Group
PACKYR: Smoking history (pack-years)

[a]Also, borderline significant three-factor interaction (see text).

****Group-by-covariate interaction; group difference, standard error (SE) and p-value not presented.

A similar, but slightly weaker interaction was observed in the analysis of the Original Comparisons versus the Ranch Hands. The general finding of insignificant group differences supported the Baseline observations (despite the use of different statistical procedures), but the followup results differed by the mild three-factor interaction.

White Blood Cell Count (WBC)

The categorical and unadjusted continuous analyses did not disclose any significant differences in WBC levels between the Ranch Hand and Comparison groups.

Covariate tests showed a borderline effect of age (with the older cohort having a slightly lower proportion of abnormally low WBC levels--4.2% versus 5.4% in the younger cohort), and the highly significant effects of race ($p<0.001$), occupation ($p=0.001$), and smoking history ($p<0.001$). Blacks had a much higher proportion of abnormally low WBC counts (15.4%) versus nonblacks (4.0%); higher proportions of enlisted flyers and enlisted groundcrew personnel (9.1% and 7.2%, respectively) had abnormally high WBC counts versus officers (3.6%). Increasing frequencies of leukocytosis were associated with increasing levels of smoking.

The adjusted categorical analysis was nonrevealing with respect to group differences, but the adjusted continuous analysis disclosed three significant three-factor interactions involving group membership: group-by-race-by-age ($p=0.005$), group-by-age-by-smoking history (pack-years; $p=0.004$), and group-by-race-by-occupation ($p=0.004$).

Further analyses were conducted stratifying by race (see Table N-2 of Appendix N). Among Blacks, the best model revealed significant group-by-occupation and group-by-age interactions ($p=0.045$, $p=0.024$, respectively). Group differences for covariate levels corresponding to young officers and young enlisted flyers were statistically significant, with the adjusted mean WBC value considerably lower in the Ranch Hand group than in the Comparison group. Conversely, the adjusted difference for the older enlisted groundcrew was in the opposite direction. The results for nonblacks were more precise: The group-by-age-by-smoking history interaction was highly significant ($p=0.002$), with young heavy smokers having a WBC level approximately 12 percent greater in the Ranch Hands than the Comparisons.

Other differences were small in magnitude and not statistically significant. Ranch Hand and Original Comparison contrasts were similar for nonblacks, but for Blacks, the group-by-occupation and group-by-age interactions did not reach statistical significance ($p=0.077$, $p=0.134$, respectively). The nonsignificance of the unadjusted and categorical adjusted analyses was equivalent to the findings at the Baseline examination. However, possibly due to different model selections, no interactions were noted at Baseline. Race and occupation were not used as covariates at Baseline.

Hemoglobin (HGB)

None of the four analyses, unadjusted and adjusted categorical tests and unadjusted and adjusted tests of mean differences, detected a significant difference between groups.

Covariate tests of association revealed the profound effects of race (8.4% abnormally low in Blacks versus 3.3% in nonblacks; p=0.002), occupation (25.1% and 25.6% abnormally high in enlisted flyers and groundcrew, respectively, versus 16.7% in officers; p<0.001), and smoking history (with proportions of abnormally high HGB levels associated with increases in pack-years of smoking; p=0.003). Continuous analyses detected significant effects of current smoking (p<0.001), occupation-by-age (p=0.002), and occupation-by-race (p=0.013) interactions. No significant group-by-covariate interactions were noted. Analysis of the Ranch Hands and Original Comparisons, however, found significant three-factor interactions of group-by-race-by-age (p=0.030) and group-by-race-by-occupation (p=0.020) (see Tables N-7 and N-8 of Appendix N). For equivalent analyses, the followup results were quite analogous to the Baseline study results.

Hematocrit (HCT)

All of the unadjusted and adjusted categorical tests and analyses of mean differences failed to detect any group differences. Since there were only five abnormally high values, this category was combined with the normal category in the categorical analyses.

The association of race to HCT was highly significant, with 4.9 percent abnormally low values noted in Blacks versus 0.9 percent in nonblacks (p<0.001). Regression analyses also detected significant effects of current smoking (p<0.001) as well as age-by-occupation (p=0.004), race-by-occupation (p=0.003), and occupation-by-smoking history (p=0.035) interactions. In both categorical and continuous adjusted analyses, no significant group-by-covariate interactions were detected. Analyses of data from the Ranch Hands and Original Comparisons, however, detected significant three-factor interactions of group-by-race-by-age (p=0.026) and group-by-race-by-occupation (p=0.011) (see Tables N-7 and N-8 of Appendix N).

Mean Corpuscular Volume (MCV)

No significant group differences were detected for MCV abnormalities or mean values by any of the unadjusted or adjusted analyses.

Main covariate effects were profound for age (p<0.001), race (p<0.001), occupation (p=0.004), and smoking history (p<0.001). The older cohort had a greater frequency of abnormally high MCV values than did the younger age group (18.0% vs. 9.4%, respectively), and Blacks had a far greater frequency of abnormally low MCV values than nonblacks (7.7% vs. 0.6%, respectively). Enlisted groundcrew personnel had a lower percentage of abnormally high values than officers or enlisted flyers (12.5%, 15.5%, and 17.0%, respectively), and increases in pack-years of smoking were associated with increasing percentages of abnormally high levels (0 pack-years: 4.7%; greater than 0 to 10 pack-years: 13.1%; and greater than 10 pack-years: 21.0%).

Continuous analyses detected significant interactions of race-by-age (p<0.001), race-by-occupation (p=0.015), and race-by-current smoking (p=0.025). The analysis of the Ranch Hand and Original Comparisons revealed a significant group-by-race interaction (p=0.031) for the categorical analyses and significant group-by-age-by-smoking history (p=0.041) and group-by-age-by-current smoking (p=0.012) interactions in the continuous

analyses. Various contrasts are given in Table N-8 of Appendix N. No explanations are apparent for these interactions except chance. The followup examination results of MCV (i.e., significant interactions) differed from the Baseline results, which showed a significantly larger adjusted mean MCV value in the Ranch Hands.

Mean Corpuscular Hemoglobin (MCH)

MCH abnormalities and mean values did not differ significantly by group in any of the unadjusted or adjusted analyses.

Main effects were very significant for all of the covariates. The older cohort had a greater frequency of abnormally high MCH values than the younger group (7.9% vs. 3.2%, respectively; $p<0.001$), while Blacks had a greater frequency of low abnormalities than nonblacks (4.9% vs. 0.3%, respectively; $p<0.001$). Enlisted groundcrew had a higher proportion of abnormalities in the lower range than enlisted flyers and officers (1.0%, 0.3%, 0.2%, respectively), but they had a lower proportion of high-range abnormalities compared to the other occupations (4.3%, 7.8%, and 7.3%, respectively). The overall p-value was 0.003. Increasing pack-years of smoking was associated with increasing frequencies of high abnormal MCH results (0 pack-years: 2.1%; greater than 0 to 10 pack-years: 6.0%; and greater than 10 pack-years: 8.3%; $p<0.001$).

Continuous analyses detected a significant race-by-age interaction ($p=0.015$), as well as significant effects of current smoking ($p<0.001$) and occupation ($p<0.001$). The followup findings did not support the Baseline observation of significantly increased MCH in the Ranch Hands, although the mean was still higher (both unadjusted and adjusted) in the Ranch Hand group.

In the analysis of the Ranch Hands and the Original Comparisons, a significant three-factor interaction of group-by-age-by-current smoking emerged ($p=0.026$). Table N-8 of Appendix N presents Ranch Hand-Comparison differences for selected covariate levels corresponding to 35- and 53-year-old nonsmokers, one-pack-per-day current smokers, and two-packs-per-day current smokers. The differences were positive for all contrasts except the 53-year-old smokers, when the differences became increasingly more negative with increasing levels of smoking.

Mean Corpuscular Hemoglobin Concentration (MCHC)

In both groups, only one abnormal MCHC count was recorded for either the abnormally low or abnormally high categories, precluding unadjusted or adjusted categorical tests, and exploration of main covariate effects. No significant group differences were detected by the unadjusted or adjusted tests of MCHC means, although race ($p=0.001$) and current smoking ($p=0.042$) were significantly associated with MCHC (higher MCHC in nonblacks and decreasing MCHC associated with increasing current levels of smoking). Similar findings were noted in the analysis of Ranch Hand and Original Comparisons, and overall, the followup findings were comparable to the 1982 Baseline MCHC results.

Platelet Count (PLT)

Neither the unadjusted nor the adjusted categorical analysis showed statistically significant group differences. Analysis of continuous data disclosed significant effects due to occupation ($p=0.039$), age ($p=0.006$), group-by-race-by-smoking history ($p<0.001$), and group-by-race-by-current smoking ($p=0.024$) interactions, with higher PLT values in the heavily smoking Ranch Hands but similar values for nonsmokers (see Table N-2 of Appendix N).

The significant interactions of group-by-race-by-smoking history ($p=0.011$) and group-by-age ($p=0.040$) were also noted for the analyses involving the Original Comparisons (see Table N-8 of Appendix N). The percentages of abnormally high PLT counts increased with increasing pack-years of smoking (0 pack-years: 0.8%; greater than 0 to 10 pack-years: 2.0%; and greater than 10 pack-years: 2.6%). Other than the interactions encountered in the adjusted analyses, the overall findings at the followup were comparable to the Baseline PLT results.

EXPOSURE INDEX ANALYSES

Exposure index analyses were conducted within each occupational cohort of the Ranch Hand group to search for dose-response relationships (see Chapter 8 for details on the exposure index). Log-linear models were fit to the categorical data to examine the effects of exposure and pack-years of smoking, as well as the interaction between these variables. The normal and abnormally high categories were pooled for the RBC count, and the abnormally low and normal response categories were pooled for MCV, MCH, and PLT due to empty cells in some strata. Because of the small numbers of abnormal values, analyses were not conducted for HCT or MCHC. The results of the unadjusted categorical analyses are presented in Table 16-7, and the counterpart adjusted analyses are given in Table 16-8.

The unadjusted analyses showed only a statistically significant result for the WBC count in the enlisted flyer category, due primarily to an excess of abnormally low values in the high exposure category. The very sparse data support a trend from low to high exposure, and the finding of abnormally low WBC counts associated with exposure is in the direction expected for an herbicide effect. However, the exposure association with abnormally low WBC counts converted to borderline significance ($p=0.082$) in the adjusted analysis. There were no statistically significant exposure level-by-smoking history interactions. Similar analyses in the other occupational strata (with much larger sample sizes) did not produce this pattern.

The unadjusted analysis of means for all eight hematological variables was carried out by a one-way analysis of variance. The results are arrayed in Table 16-9.

These analyses revealed only one statistically significant result ($p=0.038$), the RBC count in the enlisted groundcrew stratum where individuals in the medium exposure category had a higher mean RBC level than those in the low or high exposure categories. Thus, these significant RBC findings did not demonstrate a dose-response relationship. The results for HCT in the enlisted groundcrew stratum were of borderline significance ($p=0.052$) with the highest mean HCT level in the medium exposure category. In contrast to the categorical analyses, mean WBC levels in the enlisted flyers were not significantly different among the three exposure levels.

TABLE 16-7.

Unadjusted Categorical Exposure Index Analyses
for Hematological Variables by Occupation

Variable	Occupation	Exposure Index	Abnormally Low		Normal		Abnormally High		Total	p-Value
			Number	Percent	Number	Percent	Number	Percent		
RBC	Officer	Low	3	2.4	123	96.8	1	0.8	127	0.522[a]
		Medium	4	3.1	125	96.2	1	0.8	130	
		High	6	4.9	114	93.4	2	1.6	122	
	Enlisted Flyer	Low	1	1.8	54	98.2	0	0.0	55	0.401[a]
		Medium	1	1.5	64	98.5	0	0.0	65	
		High	3	5.3	54	94.7	0	0.0	57	
	Enlisted Groundcrew	Low	6	3.9	148	96.1	0	0.0	154	0.329[a]
		Medium	2	1.2	158	97.5	2	1.2	162	
		High	4	2.8	136	95.8	2	1.4	142	
WBC	Officer	Low	7	5.5	115	90.6	5	3.9	127	0.919
		Medium	7	5.4	118	90.8	5	3.8	130	
		High	5	4.1	110	90.2	7	5.7	122	
	Enlisted Flyer	Low	0	0.0	51	92.7	4	7.3	55	0.045
		Medium	1	1.6	59	92.2	4	6.2	64	
		High	6	10.5	47	82.5	4	7.0	57	
	Enlisted Groundcrew	Low	4	2.6	139	90.3	11	7.1	154	0.839
		Medium	8	4.9	142	87.6	12	7.4	162	
		High	7	4.9	125	88.0	10	7.0	142	
HGB	Officer	Low	7	5.5	100	78.7	20	15.8	127	0.425
		Medium	2	1.5	106	81.5	22	16.9	130	
		High	6	4.9	92	75.4	24	19.7	122	
	Enlisted Flyer	Low	3	5.4	36	65.4	16	29.1	55	0.350
		Medium	3	4.6	51	78.5	11	16.9	65	
		High	5	8.8	36	63.2	16	28.1	57	
	Enlisted Groundcrew	Low	5	3.2	119	77.3	30	19.5	154	0.352
		Medium	4	2.5	110	67.9	48	29.6	162	
		High	4	2.8	102	71.8	36	25.4	142	

TABLE 16-7. (continued)

Unadjusted Categorical Exposure Index Analyses
for Hematological Variables by Occupation

Variable	Occupation	Exposure Index	Abnormally Low		Normal		Abnormally High			
			Number	Percent	Number	Percent	Number	Percent	Total	p-Value
MCV	Officer	Low	1	0.8	111	87.4	15	11.8	127	0.580[b]
		Medium	1	0.8	111	85.4	18	13.8	130	
		High	0	0.0	102	83.6	20	16.4	122	
	Enlisted Flyer	Low	0	0.0	43	78.2	12	21.8	55	0.764[b]
		Medium	0	0.0	54	83.1	11	16.9	65	
		High	0	0.0	47	82.5	10	17.5	57	
	Enlisted Groundcrew	Low	2	1.3	139	90.3	13	8.4	154	0.091[b]
		Medium	3	1.8	133	82.1	26	16.0	162	
		High	3	2.1	117	82.4	22	15.5	142	
MCH	Officer	Low	1	0.8	117	92.1	9	7.1	127	0.916[b]
		Medium	0	0.0	121	93.1	9	6.9	130	
		High	0	0.0	112	91.8	10	8.2	122	
	Enlisted Flyer	Low	0	0.0	51	92.7	4	7.3	55	0.855[b]
		Medium	0	0.0	60	92.3	5	7.7	65	
		High	0	0.0	54	94.7	3	5.3	57	
	Enlisted Groundcrew	Low	1	0.6	147	95.4	6	3.9	154	0.626[b]
		Medium	2	1.2	151	93.2	9	5.6	162	
		High	3	2.1	130	91.6	9	6.3	142	
PLT	Officer	Low	2	1.6	120	94.5	5	3.9	127	0.487[b]
		Medium	1	0.8	126	97.7	2	1.6	129	
		High	0	0.0	119	97.5	3	2.5	122	
	Enlisted Flyer	Low	1	1.8	51	92.7	3	5.4	55	0.135[b]
		Medium	0	0.0	64	98.5	1	1.5	65	
		High	0	0.0	57	100.0	0	0.0	57	
	Enlisted Groundcrew	Low	0	0.0	152	98.7	2	1.3	154	0.914[b]
		Medium	1	0.6	158	97.5	3	1.8	162	
		High	0	0.0	140	98.6	2	1.4	142	

[a]Normal pooled with abnormally high.

[b]Abnormally low pooled with normal.

TABLE 16-8.

Adjusted Categorical Exposure Index Analyses (Log-Linear Models) for Hematological Variables by Occupation (p-Values)

Variable	Occupation	Exposure Index Effect*	Smoking History Effect**	Exposure Index-by-Smoking History
RBC	Officer	0.593	0.246	0.472
	Enlisted Flyer	0.552	0.364	0.981
	Enlisted Groundcrew	0.310	0.515	0.717
WBC	Officer	0.928	0.001	0.616
	Enlisted Flyer	0.082	0.121	0.971
	Enlisted Groundcrew	0.761	0.009	0.104
HGB	Officer	0.444	0.393	0.424
	Enlisted Flyer	0.413	0.647	0.980
	Enlisted Groundcrew	0.299	0.104	0.143
MCV	Officer	0.718	<0.001	0.334
	Enlisted Flyer	0.619	0.020	0.490
	Enlisted Groundcrew	0.101	0.028	0.574
MCH	Officer	0.852	0.002	0.777
	Enlisted Flyer	0.800	0.168	0.514
	Enlisted Groundcrew	0.681	0.288	0.530
PLT	Officer	0.410	0.099	0.708
	Enlisted Flyer	0.178	0.816	0.976
	Enlisted Groundcrew	0.910	0.363	0.996

*Adjusted for smoking history (no interaction).

**Adjusted for exposure index (no interaction).

TABLE 16-9.

Unadjusted Continuous Exposure Index Analyses for Hematological Variables by Occupation (Analysis of Variance)

Occupation	Variable	Exposure Index Mean ± SE			p-Value
		Low	Medium	High	
		(n=127)	(n=130)	(n=122)	
Officer	RBC	4.904±0.030	4.861±0.029	4.899±0.034	0.560
	WBC[a]	6.488	6.553	6.753	0.512
	HGB	15.468±0.084	15.463±0.087	15.593±0.094	0.507
	HCT	45.379±0.243	45.313±0.255	45.791±0.284	0.380
	MCV	92.648±0.430	93.260±0.365	93.548±0.367	0.252
	MCH	31.606±0.161	31.851±0.134	31.884±0.123	0.314
	MCHC	34.090±0.060	34.123±0.060	34.067±0.059	0.801
	PLT[a]	253.66	255.70[b]	256.72	0.799
		(n=55)	(n=65)	(n=57)	
Enlisted Flyer	RBC	4.972±0.048	4.942±0.037	4.957±0.053	0.894
	WBC[a]	7.531	7.236	6.966	0.378
	HGB	15.785±0.149	15.629±0.110	15.721±0.180	0.744
	HCT	46.345±0.425	45.908±0.315	46.300±0.535	0.717
	MCV	93.269±0.618	92.923±0.501	93.400±0.572	0.817
	MCH	31.782±0.222	31.675±0.187	31.735±0.208	0.933
	MCHC	34.065±0.075	34.058±0.072	33.956±0.072	0.508
	PLT[a]	272.87	275.34[c]	261.13	0.382
		(n=154)	(n=162)	(n=142)	
Enlisted Groundcrew	RBC	4.990±0.032	5.094±0.031	4.999±0.033	0.038
	WBC[a]	7.185	7.236	7.389	0.686
	HGB	15.566±0.099	15.807±0.075	15.685±0.090	0.147
	HCT	45.740±0.284	46.580±0.210	46.086±0.252	0.052
	MCV	91.737±0.399	91.672±0.404	92.376±0.458	0.436
	MCH	31.251±0.154	31.138±0.151	31.468±0.166	0.325
	MCHC	34.032±0.059	33.941±0.051	34.031±0.057	0.409
	PLT[a]	270.97	273.42	268.27	0.748

[a] Standard errors (SE) not presented, since variables were analyzed on logarithmic scale.

[b] n=129.

[c] n=64.

Adjusted analyses of the differences in variable means were performed by regression techniques. As in the unadjusted analysis, RBC and HCT in the enlisted groundcrew stratum presented contrasts of interest for the medium versus low exposure categories (p=0.059, and p=0.041, respectively). Further, it was noted that smoking history (pack-years) was significantly associated with the RBC and HCT variables in a negative direction, while the current smoking covariate (cigarettes/day) showed a positive trend.

By linear models, the adjusted exposure analyses included the main effects of the covariates, as well as interactions between exposure level and each covariate. No clear dose-response relationships were identified, but eight exposure-by-covariate interactions were noted, and these are reflected in summary form in Table 16-10. Analyses exploring these interactions are presented in Table N-3 of Appendix N.

These data do not disclose any interpretable pattern of occupational predominance in the Ranch Hand group. However, the relative sparseness of the enlisted groundcrew stratum in these interactions is noteworthy, as is the relative representation of race and age as interactive covariates.

Exposure contrasts are shown in Table N-3 of Appendix N. For HGB and HCT, high versus low contrasts were significant at covariate levels corresponding to Black officers, and medium versus low contrasts were significant at covariate levels corresponding to enlisted flyers, age 35. The medium versus low contrast corresponding to Black enlisted groundcrew was also significant for PLT.

In summary, several interactions were detected in the continuous analyses, but only a few of the main effect exposure analyses demonstrated statistical significance. Of these, only one showed a weak linear trend of effects increasing from low to high exposure. No pattern of exposure effects was discernible by occupational category.

TABLE 16-10.

Summary of Exposure Index-by-Covariate Interactions Encountered in Adjusted Continuous Analyses of Hematological Variables (General Linear Models)

Variable	Occupation	Covariate	p-Value
RBC	Officer	Race	0.052
RBC	Enlisted Flyer	Age	0.012
HGB	Officer	Race	0.034
HGB	Enlisted Flyer	Age	<0.001
HCT	Officer	Race	0.048
HCT	Enlisted Flyer	Age	0.002
PLT	Enlisted Flyer	Current Smoking	0.050
PLT	Enlisted Groundcrew	Race	0.044

LONGITUDINAL ANALYSES

The sample data base for the longitudinal analyses was the number of participants who attended both examinations (971 Ranch Hands and 1,139 Comparisons). These variables were analyzed: MCV, MCH, and PLT. The results of these analyses are depicted in Table 16-11.

These analyses showed no statistically significant group differences for the MCV and MCH variables, whereas a highly significant group difference was present for mean PLT counts. Both MCV and MCH counts increased symmetrically from the Baseline examination, a fact likely attributable to an ongoing effect of smoking (see Table 16-4) or to a laboratory technique difference. The highly significant difference (p=0.002) for PLT counts was due to a group-by-examination time interaction, with the Ranch Hands exhibiting a slight decline in the mean PLT value from the Baseline to followup examination, whereas the Comparisons showed a slight increase in the mean PLT value. No biological significance is assigned to the statistically significant group difference in the change in PLT counts. Based upon the results of the longitudinal analysis, there is reasonable equivalence of the hematological status between the two groups.

TABLE 16-11.

Longitudinal Analyses for MCV, MCH, and PLT:
A Contrast of Baseline and First Followup Examination Test Means

			Means				
Variable	Group	Total	1982 Baseline	1985 Followup	Difference (Followup-Baseline)	Error*	p-Value (Equality of Difference)
MCV	Ranch Hand	971	88.89	92.60	+3.71	2.800	0.96
	Comparison	1,139	88.68	92.38	+3.70		
MCH	Ranch Hand	971	30.81	31.55	+0.74	0.879	0.30
	Comparison	1,139	30.65	31.45	+0.80		
PLT	Ranch Hand	971	276.9	271.5	-5.4	35.38	0.002
	Comparison	1,139	266.7	268.2	+1.5		

*Error = $\sqrt{\text{Subj * Time/Group mean squares.}}$

SUMMARY AND CONCLUSIONS

The functional integrity of the hematopoietic system was assessed by the measurement of eight peripheral blood variables: red blood cell count (RBC), white blood cell count (WBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count (PLT). These variables were analyzed in the discrete form to detect differences in the percentages of values outside the designated laboratory range, as well as in the continuous form to detect shifts in mean values between the two groups. A summary of all of these analyses, unadjusted and adjusted for the covariates of age, race, occupation, and smoking, is presented in Table 16-12.

The unadjusted discrete analysis of the percent abnormal values, both low and high, showed no statistically significant differences between the Ranch Hand and Comparison groups for any of the hematological variables. Similarly, the adjusted categorical analysis disclosed that none of the adjusted relative risks was significant for either group, and that no significant group-by-covariate interactions were present.

The unadjusted continuous analysis did not detect any significant differences in group means for any of the eight variables. The adjusted continuous analysis found no significant group differences for HGB, HCT, MCV, MCH, and MCHC, but encountered significant three-factor interactions for WBC (group-by-race-by-age, group-by-age-by-smoking history, and group-by-race-by-occupation), for PLT (group-by-race-by-smoking history and group-by-race-by-current level of smoking), and a borderline interaction for RBC (group-by-occupation-by-smoking history). Ranch Hand versus Original Comparison analyses revealed further significant interactions for HGB, HCT, MCV, and MCH. As no group strata demonstrated consistent patterns of hematologic impairment, biologic relevance was not assigned to the interactions. The covariate effects of age, race, occupation, and smoking history were highly significant for many of the hematological variables.

The effect of race was particularly profound for all variables except PLT. There was fair consistency in the covariate effects upon the RBC-related variables. Generally, decreasing hematologic values were associated with increasing age and the Black race, and increasing hematologic values were associated with increasing smoking. The detection of these classical covariate effects lends credence to the overall finding of nonsignificant group differences for all of the hematological variables. Significant group differences found for MCV and MCH at the Baseline examination were not significant at the first followup. Other differences (e.g., covariate effects, interactions) between the Baseline and followup examinations may be due to small numeric shifts in the cohorts under study (see Chapter 2) and the selection of alternate statistical models, or due to chance.

Unadjusted continuous exposure analyses in the Ranch Hand group revealed only one significant effect (RBC in enlisted groundcrew) and one borderline effect (HCT in enlisted groundcrew), but neither was consistent with a plausible dose-response relationship. The adjusted continuous exposure analyses found only one significant contrast (HCT, medium exposure versus low exposure, enlisted groundcrew). However, seven exposure level-by-covariate interactions were noted for four of the hematological variables. Discrete outcome analyses of the exposure level index revealed a significant result only for WBC in the enlisted flyers.

TABLE 16-12.

Overall Summary Results of Unadjusted and Adjusted Analyses of Hematological Variables

	Unadjusted		Adjusted	
	Mean	Categorical	Mean	Categorical
RBC	NS	NS	NS*	NS
WBC	NS	NS	****	NS
HGB	NS	NS	NS	NS
HCT	NS	NS	NS	NS
MCV	NS	NS	NS	NS
MCH	NS	NS	NS	NS
MCHC	NS	--	NS	--
PLT	NS	NS	****	NS

NS: Not sgnificant ($p>0.10$).

NS*: Borderline significant group-by-covariate interaction ($0.05 \leq p < 0.10$).

--Analysis not performed due to sparse data.

****Group-by-covariate interaction.

Note: Significant group-by-covariate interaction, Ranch Hands versus Original Comparisons only, for HGB, HCT, MCV, and MCH.

The longitudinal analyses of MCV, MCH, and PLT found significant differences only for PLT values between the Baseline and followup examinations, with the Baseline group difference in mean values closing to near equivalence at the followup examination.

In conclusion, none of the eight hematological variables were found to differ significantly between the Ranch Hand and Comparison groups. In fact, group equivalence was more apparent at the followup examination than at the Baseline examination. The classical effects of age, race, and smoking were demonstrated with most of the hematological variables. The longitudinal analyses also suggested that neither group manifested an impairment of the hematopoietic system. Exposure index analyses did not support a plausible dose-response relationship for any of the hematological variables.

CHAPTER 16

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