CHAPTER 16

HEMATOLOGIC EVALUATION

INTRODUCTION

Background

Animal experiments have confirmed both direct and indirect hematopoietic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or dioxin). Although direct impairment of the hematopoietic system may result from exposure to chlorophenols or dioxin, marked abnormalities in many of the circulating hematologic elements may also be due to the severe toxicity observed in other organs or organ systems. In a study of monkeys, using single low and high doses of TCDD, early hematologic effects included increased neutrophil counts in the low-dose group, and lymphopenia and thrombocytopenia in the high-dose group.[1] At the end of the experiment, half of 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.[2] 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 ug/kg demonstrated depressed red blood cell counts and packed cell volumes in the high-dose group.[3] 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.[4] Thrombocytopenia and hemoconcentration were found in rats. Because of the lymphopenia in mice and guinea pigs, TCDD was judged to be immunosuppressive. A discussion of cellular immune function is included in Chapter 19 of this report.

In general, human observational studies showed 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.[5] 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.[6,7]

Two contemporary morbidity studies[8,9] of the Nitro, West Virginia, accident included routine 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 hematologic results in their publications; presumably, there were no significant differences in any of the parameters between the exposed and the unexposed cohorts.

Two pilot studies of TCDD-contaminated residential areas in Missouri also included routine hematologic assays of peripheral blood.[10,11] One study

paradoxically noted a significantly increased mean platelet count in the high-risk group, although the data were not adjusted for smoking.[10] The Quail Run study, predominantly emphasizing cell-mediated immunity, found a significantly higher proportion of individuals with white blood cell counts (WBC) exceeding 10,000/mm^3 in the exposed group. They also found significant group differences in the mean leukocyte count, mean absolute granulocyte count, and the mean percentage of monocytes in the differential count,[11] but the authors did not identify the group (exposed or unexposed) that had the abnormal hematologic findings.

Baseline Summary Results

The functional integrity of the hematopoietic system was assessed at the Baseline examination by the measurement of eight peripheral blood variables: red blood cell count (RBC), WBC, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelet count. 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.

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., RBC, WBC, hemoglobin, hematocrit, MCHC, and platelet count were nearly identical to the adjusted means of the Comparison group, and all were well within normal range. The percent of abnormal values for these eight variables, as established by the upper and lower limits of normal, did not differ significantly between the two groups.

Linear models demonstrated the profound effect of lifetime smoking (measured in pack-years). With increased smoking, white blood cell, hemoglobin, hematocrit, MCV, MCH, and platelet values increased, whereas the MCHC decreased. The RBC revealed a borderline significant negative relationship to smoking. No statistically significant group-by-lifetime smoking interactions were detected.

The exposure index analyses conducted within the Ranch Hand group disclosed two statistically significant exposure index effects as well as seven significant or borderline significant exposure index-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 between the hematologic 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 generally consistent, and that adverse health effects related to herbicides were not present.

1985 Followup Study Summary Results

The same peripheral blood variables were analyzed in the 1985 followup. 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 hematologic variables. Similarly, in the adjusted discrete analyses, none of the adjusted relative risks was significant, and there were no significant group-by-covariate interactions.

The unadjusted continuous analyses 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 hemoglobin, hematocrit, MCV, MCH, and MCHC, but encountered significant three-factor interactions for WBC (group-by-race-by-age, group-by-age-by-lifetime smoking history, and group-by-race-by-occupation) and platelet count (group-by-race-by-lifetime smoking history and group-by-race-by-current level of smoking), and a borderline interaction for RBC (group-by-occupation-by-lifetime smoking history). Ranch Hand versus Original Comparison analyses revealed further significant interactions for hemoglobin, hematocrit, MCV, and MCH. As no subgroup demonstrated consistent patterns of hematologic impairment, biologic relevance was not assigned to the interactions. The significant group differences found for MCV and MCH at the Baseline examination were not present in the 1985 followup analyses. The covariate effects of age, race, occupation, and lifetime smoking history were highly significant for many of the hematologic variables.

The effect of race was particularly profound for all variables except platelet count. 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 lifetime and current smoking.

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

The longitudinal analyses of MCV, MCH, and platelet count found a significant difference for platelet count, with the Ranch Hands having an average decrease in platelet count between examinations and the Comparisons an average increase. As a result, the Baseline group difference (nonsignificant) in mean values closed to near equivalence at the followup examination.

In conclusion, none of the eight hematologic variables was found to differ significantly between the Ranch Hand and Comparison groups. The expected effects of age, race, and smoking were demonstrated with most of the hematologic 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 hematologic variables.

Parameters of the 1987 Hematologic Evaluation

Dependent Variables

The analysis of the 1987 hematologic evaluation consisted of data from the laboratory examination only. No questionnaire or physical examination data were analyzed.

Laboratory Examination Data

Eight hematologic variables measured at the laboratory examination were analyzed--RBC (million/cubic mm), WBC (thousand/cubic mm), hemoglobin (gm/dl), hematocrit (percent), MCV (cubic micra), MCH (micromicrogram), MCHC (gm/dl), and platelet count (thousand/cubic mm). These variables were determined by routine hematologic procedures. All dependent variables were analyzed in both the discrete and continuous forms.

The Scripps Clinic and Research Foundation (SCRF) laboratory coefficients of variation for these variables met or exceeded strict 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). These SCRF laboratory normal values are given in Table 16-1.

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 these variables.

Covariates

The effects of age, race, occupation, current level of cigarette smoking (cigarettes/day), and lifetime cigarette smoking history (pack-years) were examined in the hematologic evaluation, both in pairwise associations with the dependent variables and in adjusted statistical analyses. Age, race, and occupation are matching variables and were used in analyses with all dependent variables. A discretized form of the lifetime cigarette smoking history covariate was used in the discrete analysis of the dependent variables. Both the current level of cigarette smoking and the lifetime cigarette smoking history covariates were used in the continuous analyses of the dependent variables. In continuous analyses, age and the two smoking variables were used in the continuous form.

Relation to Baseline and 1985 Followup Studies

The eight variables analyzed in the 1987 followup were also analyzed in the Baseline and 1985 followup studies.

TABLE 16-1.

Statistical Analysis for the Hematologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Red Blood Cell Count (RBC) (million/cubic mm)	LAB	D/C	Abnormal Low: <4.3 Normal: 4.3-5.9 Abnormal High: >5.9	AGE RACE OCC CSMOK PACKYR	UC:CS,TT AC:LL,GLM CA:CC,TT,GLM CS,FT UE:CS,FT,GLM AE:LL,GLM
White Blood Cell Count (WBC) (thousand/cubic mm)	LAB	D/C	Abnormal Low: <4.5 Normal: 4.5-11.0 Abnormal High: >11.0	AGE RACE OCC CSMOK PACKYR	UC:CS,TT AC:LL,GLM CA:CC,TT,GLM CS,FT UE:CS,FT,GLM AE:LL,GLM
Hemoglobin (gm/dl)	LAB	D/C	Abnormal Low: <13.9 Normal: 13.9-18.0 Abnormal High: >18.0	AGE RACE OCC CSMOK PACKYR	UC:CS,TT AC:LL,GLM CA:CC,TT,GLM CS,FT UE:CS,FT,GLM AE:LL,GLM
Hematocrit (percent)	LAB	D/C	Abnormal Low: <39.0 Normal: 39.0-55.0 Abnormal High: >55.0	AGE RACE OCC CSMOK PACKYR	UC:CS,TT AC:LL,GLM CA:CC,TT,GLM CS,FT UE:CS,FT,GLM AE:LL,GLM
Mean Corpuscular Volume (MCV) (cubic micra)	LAB	D/C	Abnormal Low: <80.0 Normal: 80.0-97.0 Abnormal High: >97.0	AGE RACE OCC CSMOK PACKYR	UC:CS,TT AC:LL,GLM CA:CC,TT,GLM CS,FT UE:CS,FT,GLM AE:LL,GLM L:RM

TABLE 16-1. (continued)

Statistical Analysis for the Hematologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Mean Corpuscular Hemoglobin (MCH) (micromicrogram)	LAB	D/C	Abnormal Low: <26.0 Normal: 26.0-34.0 Abnormal High: >34.0	AGE RACE OCC CSMOK PACKYR	UC:CS,TT AC:LL,GLM CA:CC,TT,GLM CS,FT UE:CS,FT,GLM AE:LL,GLM L:RM
Mean Corpuscular Hemoglobin Concentration (MCHC) (gm/dl)	LAB	D/C	Abnormal Low: <31.0 Normal: 31.0-37.0 Abnormal High: >37.0	AGE RACE OCC CSMOK PACKYR	UC:CS,TT AC:LL,GLM CA:CC,TT,GLM CS,FT UE:CS,FT,GLM AE:LL,GLM
Platelet Count (thousand/cubic mm)	LAB	D/C	Abnormal Low: <130 Normal: 130-400 Abnormal High: >400	AGE RACE OCC CSMOK PACKYR	UC:CS,TT AC:LL,GLM CA:CC,TT,GLM CS,FT UE:CS,FT,GLM AE:LL,GLM L:RM

Covariates

Variable (Abbreviations)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born >1942 Born 1923-1941 Born ≤1922
Race (RACE)	MIL	D	Nonblack Black

TABLE 16-1. (continued)

Statistical Analysis for the Hematologic Assessment

Covariates

(Abbreviations)	Data Source	Data Form	Variable Cutpoints
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Current Cigarette Smoking (CSMOK) (cigarettes/day)	Q-SR	D/C	0-Never 0-Former >0-20 >20
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	D/C	0 >0-10 >10

Abbreviations:

Data Source:
LAB--1987 SCRF laboratory results
MIL--Air Force military records
Q-SR--1987 NORC questionnaire (self-reported)

Data Form:
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:
UC--Unadjusted core analyses
AC--Adjusted core analyses
CA--Dependent variable-covariate associations
UE--Unadjusted exposure index analyses
AE--Adjusted exposure index analyses
L--Longitudinal analyses

Statistical Methods:
CC--Pearson's product moment correlation coefficient
CS--Chi-square contingency table test
FT--Fisher's exact test
GLM--General linear models analysis
LL--Log-linear models analysis
RM--Repeated measures analysis
TT--Two-sample t-test

Statistical Methods

The basic statistical analysis methods used in the hematologic evaluation are described in Chapter 7. Table 16-1 summarizes the statistical analyses performed for the 1987 hematologic evaluation. The first part of this table describes the dependent variables analyzed. The second part of this table provides a further description of candidate covariates examined. Abbreviations are used extensively in the body of the table and are defined in footnotes. Table 16-2 provides a list of the number of participants excluded and reasons for exclusion by group, as well as the number of participants with missing data for the dependent variables described in Table 16-1.

RESULTS

Ranch Hand and Comparison Group Contrast

Laboratory Examination Variables

Table 16-3 contains the results of the unadjusted analyses, both continuous and discrete, for the eight hematologic variables. The results from the continuous analysis of each variable are presented first; these include the sample size, mean, and 95 percent confidence interval for the mean in each of the Ranch Hand and Comparison groups, together with the p-value from a test of the significance of the difference in the means between the groups. These are followed by the results from the discrete analyses, which includes the percentage of individuals in each group with abnormally low, normal, and abnormally high values (according to the cutpoints given in Table 16-1) in each group. Note that for the discrete analyses an overall p-value is given, as well as estimated relative risks, confidence intervals, and p-values for abnormally low versus normal and abnormally high versus normal contrasts.

Appendix M, Table M-1, contains the results from examination of the pairwise associations between each of the hematologic variables and the covariates. Table 16-4 gives the results of the continuous and discrete group comparison adjusted for these covariates. A similar format is used except that the adjusted discrete analyses give only the sample size in each group and not the distributions of percentages.

RBC

There were no statistically significant unadjusted differences in RBC between the groups, either in terms of the mean RBC levels ($p=0.333$) or the percent with abnormally low or abnormally high values ($p=0.510$).

RBC was significantly associated with age ($p<0.001$ for both continuous and discrete analyses), race ($p=0.012$ and $p<0.001$ for continuous and discrete analyses, respectively), occupation ($p<0.001$, continuous analysis), lifetime cigarette smoking ($p=0.003$, discrete analysis), and current cigarette smoking ($p<0.001$, continuous analysis). RBC was negatively correlated with age

TABLE 16-2.

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

Variable	Analysis Use	Group		Total
		Ranch Hand	Comparison	
RBC	DEP	1	3	4
WBC	DEP	2	3	5
Hemoglobin	DEP	1	3	4
Hematocrit	DEP	1	3	4
MCV	DEP	1	3	4
MCH	DEP	1	3	4
MCHC	DEP	1	3	4
Platelet Count	DEP	2	3	5
Temperature $\geq$ 100°F at Physical Examination	EXC	1	3	4

Abbreviations: DEP--Dependent variable (missing data)
EXC--Exclusion

TABLE 16-3.

Unadjusted Analysis for Hematologic Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Est. Relative Risk (95% C.I.)	p-Value
RBC	n	993	1,293			
	Mean	4.939	4.954		—	0.333
	95% C.I.	(4.915,4.963)	(4.934,4.975)			
	Number/%					
	Low	37 3.7%	48 3.7%	Overall		0.510
	Normal	948 95.5%	1,228 95.0%	Low vs. Normal	1.00 (0.64,1.55)	0.992
	High	8 0.8%	17 1.3%	High vs. Normal	0.61 (0.26,1.42)	0.250
WBC	n	992	1,293			
	Mean*	6.875	6.703		—	0.038
	95% C.I.*	(6.752,7.000)	(6.599,6.809)			
	Number/%					
	Low	55 5.5%	91 7.0%	Overall		0.260
	Normal	886 89.3%	1,127 87.2%	Low vs. Normal	0.77 (0.54,1.09)	0.136
	High	51 5.1%	75 5.8%	High vs. Normal	0.86 (0.60,1.25)	0.435
Hemoglobin	n	993	1,293			
	Mean	15.677	15.662		—	0.741
	95% C.I.	(15.605,15.749)	(15.605,15.719)			
	Number/%					
	Low	40 4.0%	50 3.9%	Overall		0.975
	Normal	939 94.6%	1,224 94.7%	Low vs. Normal	1.04 (0.68,1.59)	0.849
	High	14 1.4%	19 1.5%	High vs. Normal	0.96 (0.48,1.93)	0.912
Hematocrit	n	993	1,293			
	Mean	45.201	45.175		—	0.850
	95% C.I.	(44.995,45.407)	(45.009,45.342)			
	Number/%					
	Low	20 2.0%	27 2.1%	Overall[a]		0.999
	Normal	969 97.6%	1,265 97.8%	Low vs. Normal/ High	0.96 (0.54,1.73)	0.904
	High	4 0.4%	1 0.1%			

TABLE 16-3. (continued)

Unadjusted Analysis for Hematologic Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Est. Relative Risk (95% C.I.)	p-Value
MCV	n	993	1,293			
	Mean	91.613	91.315		—	0.151
	95% C.I.	(91.305,91.920)	(91.050,91.581)			
	Number/%					
	Low	12 1.2%	16 1.2%	Overall		0.766
	Normal	871 87.7%	1,146 88.6%	Low vs. Normal	0.99 (0.46,2.10)	0.968
	High	110 11.1%	131 10.1%	High vs. Normal	1.10 (0.84,1.44)	0.465
MCH	n	993	1,293			
	Mean	31.795	31.686		—	0.150
	95% C.I.	(31.682,31.907)	(31.589,31.783)			
	Number/%					
	Low	7 0.7%	7 0.5%	Overall		0.882
	Normal	907 91.3%	1,184 91.6%	Low vs. Normal	1.30 (0.46,3.74)	0.617
	High	79 8.0%	102 7.9%	High vs. Normal	1.01 (0.74,1.37)	0.944
MCHC	n	993	1,293			
	Mean	34.681	34.672		—	0.715
	95% C.I.	(34.645,34.716)	(34.643,34.701)			
	Number/%					
	Low	0 0.0%	0 0.0%	Overall	—	—
	Normal	993 100.0%	1,293 100.0%	Low vs. Normal	—	—
	High	0 0.0%	0 0.0%	High vs. Normal	—	—
Platelet Count	n	992	1,293			
	Mean	265.47	259.62		—	0.017
	95% C.I.	(261.76,269.19)	(256.53,262.70)			
	Number/%					
	Low	4 0.4%	4 0.3%	Overall[b]		0.035
	Normal	959 96.7%	1,269 98.1%	High vs. Normal/	1.92 (1.08,3.41)	0.027
	High	29 2.9%	20 1.6%	Low		

*Transformed from natural logarithm scale.

[a]High pooled with normal.

[b]Low pooled with normal.

—Estimated relative risk not applicable for continuous analysis of a variable; estimated relative risk/ confidence interval not given due to cells with zero frequency.

TABLE 16-4.

Adjusted Analysis for Hematologic Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
RBC	n	993	1,293				AGE (p<0.001)
	Adj. Mean	4.935	4.952		—	0.284	OCC (p<0.001)
	95% C.I.	(4.911,4.960)	(4.931,4.974)				CSMOK (p<0.001)
							PACKYR (p=0.015)
	n	993	1,293	Overall		0.757	AGE (p<0.001)
				Low vs. Normal	1.02 (0.67,1.54)	0.936	RACE (p<0.001)
				High vs. Normal	0.77 (0.38,1.55)	0.459	PACKYR (p=0.023)
WBC	n	992	1,293				AGE*PACKYR (p=0.013)
	Adj. Mean*	6.567	6.485		—	0.214	RACE*PACKYR (p=0.014)
	95% C.I.*	(6.388,6.752)	(6.314,6.661)				OCC*CSMOK (p=0.003)
							CSMOK*PACKYR (p<0.001)
	n	992	1,293	Overall		0.357	AGE*RACE (p=0.024)
				Low vs. Normal	0.80 (0.57,1.12)	0.201	PACKYR (p<0.001)
				High vs. Normal	0.87 (0.62,1.24)	0.453	
Hemoglobin	n	993	1,293				CSMOK (p<0.001)
	Adj. Mean	15.556	15.566		—	0.810	AGE*RACE (p=0.008)
	95% C.I.	(15.411,15.701)	(15.425,15.708)				RACE*OCC (p=0.004)
							RACE*PACKYR (p=0.050)
	n	993	1,293	Overall		0.938	AGE*OCC (p=0.012)
				Low vs. Normal	1.08 (0.72,1.62)	0.726	RACE (p<0.001)
				High vs. Normal	1.03 (0.56,1.90)	0.928	

TABLE 16-4. (continued)

Adjusted Analysis for Hematologic Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Hematocrit	n Adj. Mean 95% C.I.	993 45.086 (44.667,45.505)	1,293 45.142 (44.733,45.550)		—	0.662	CSMOK (p<0.001) AGE*RACE (p=0.007) RACE*OCC (p=0.011) RACE*PACKYR (p=0.040)
	n	993	1,293	Overall[a] Low vs. Normal/ High	1.03 (0.60,1.75)	0.920 0.920	AGE (p=0.022) RACE (p<0.001)
MCV	n Adj. Mean 95% C.I.	993 90.502 (89.957,91.048)	1,293 90.316 (89.789,90.842)		—	0.342	AGE*RACE (p=0.002) AGE*PACKYR (p=0.015) RACE*PACKYR (p=0.050) OCC*CSMOK (p=0.002) CSMOK*PACKYR (p<0.001)
	n	993	1,293	Overall Low vs. Normal High vs. Normal	 1.09 (0.57,2.11) 1.10 (0.84,1.44)	0.757 0.787 0.490	AGE (p=0.002) RACE (p<0.001) PACKYR (p<0.001)
MCH	n Adj. Mean 95% C.I.	993 31.170 (30.987,31.352)	1,293 31.096 (30.921,31.270)		—	0.305	AGE*RACE (p=0.025) AGE*PACKYR (p=0.021) OCC*CSMOK (p=0.006) CSMOK*PACKYR (p=0.002)
	n	993	1,293	Overall Low vs. Normal High vs. Normal	 1.34 (0.60,3.01) 1.01 (0.75,1.37)	0.780 0.478 0.928	AGE (p<0.001) RACE (p<0.001) PACKYR (p<0.001)

TABLE 16-4. (continued)

Adjusted Analysis for Hematologic Variables by Group

Variable	Statistic	Group: Ranch Hand	Group: Comparison	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
MCHC	n Adj. Mean 95% C.I.	993 34.484 (34.430,34.538)	1,293 34.472 (34.420,34.523)		—	0.588	AGE (p<0.001) RACE (p<0.001) OCC (p=0.007) CSMOK (p<0.001)
Platelet Count	n Adj. Mean 95% C.I.	992 264.77 (261.05,268.49)	1,293 259.06 (255.75,262.37)		—	0.018	OCC (p=0.035) AGE*PACKYR (p=0.050)
	n	992	1,293	Overall[b] High vs. Normal/ Low	1.92 (1.08,3.41)	0.035 0.027	None

*Transformed from natural logarithm scale.

[a]High pooled with normal.

[b]Low pooled with normal.

—Adjusted relative risk not applicable for continuous analysis of a variable.

(r=-0.141); correspondingly, the percent with abnormally low values increased with age (2.3% for those born in or after 1942, 4.2% for those born between 1923 and 1941, and 11.9% for those born in or before 1922). Blacks had a higher mean value (5.03 million/cubic mm) and higher percentages of both abnormally low (8.0%) and abnormally high (6.6%) values than nonblacks (mean=4.94 million/cubic mm, percent abnormally low=3.4%, and percent abnormally high=0.7%). The mean RBC count was higher in enlisted flyers than in officers and highest in the enlisted groundcrew (mean=4.94, 4.88, and 5.00 million/cubic mm, respectively). Greater than 10 pack-year smokers had a higher percentage of abnormally low values (5.2%) than at most 10 pack-year smokers (2.5%) and nonsmokers (2.6%). The correlation of RBC with current cigarette smoking was positive (r=0.093) and highly statistically significant, but small in magnitude.

Contrast of the group means adjusted for covariates detected significant effects of age ($p<0.001$), occupation ($p<0.001$), lifetime cigarette smoking history ($p=0.015$), and current cigarette smoking ($p<0.001$), but the group difference was not statistically significant ($p=0.284$). Adjusted discrete analyses detected significant effects of age ($p<0.001$), race ($p<0.001$), and lifetime cigarette smoking history ($p=0.023$), but no significant group effect ($p=0.757$), with adjusted relative risks near or less than 1.

WBC

The distribution of WBC was strongly skewed to the right in each group and thus continuous analyses were conducted on a logarithmic scale. The undjusted mean log WBC was significantly higher in the Ranch Hand group than in the Comparison group ($p=0.038$); geometric means obtained by transforming back to the original scale were 6.875 and 6.703 thousand per cubic mm, respectively. There were no statistically significant differences in the discrete analysis ($p=0.260$).

Race, occupation, lifetime cigarette smoking history, and current cigarette smoking were all statistically significant covariates ($p<0.001$ in all cases [continuous and discrete], except for occupation, which was significant in the continuous analysis only). Blacks had a lower mean count than nonblacks (6.05 vs. 6.83 thousand per cubic mm), and 19.0 percent of the Blacks versus 5.6 percent of the nonblacks had abnormally low levels. Officers had a lower mean count than enlisted flyers or enlisted groundcrew (6.34, 7.09, and 7.05 thousand per cubic mm, respectively). WBC increased significantly with both lifetime and current cigarette smoking (r=0.309 and r=0.510, respectively). Correspondingly, the percent of individuals with abnormally low levels decreased and the percent with abnormally high levels increased as lifetime and current cigarette smoking levels increased (9.4%, 6.7%, and 4.4% abnormally low for nonsmokers, at most 10 pack-year smokers, and greater than 10 pack-year smokers, respectively; 0.5%, 2.0%, 13.8%, and 13.9% abnormally high for nonsmokers, former smokers, at most 20 cigarettes per day current smokers, and greater than 20 cigarettes per day current smokers, respectively).

In the adjusted continuous analysis there were several interactions among the covariates: age-by-lifetime cigarette smoking history ($p=0.013$), race-by-lifetime cigarette smoking history ($p=0.014$), occupation-by-current

cigarette smoking (p=0.003), and current cigarette smoking-by-lifetime cigarette smoking history (p<0.001). The adjusted mean WBC counts were not significantly different between the Ranch Hand and Comparison groups, however (p=0.214). Adjusted discrete analysis detected a significant age-by-race interaction (p=0.024) and a significant effect of lifetime cigarette smoking history (p<0.001), but the group difference was not statistically significant (p=0.357); adjusted relative risks for individual contrasts were less than 1.

Hemoglobin

Neither continuous nor discrete unadjusted analyses revealed any significant group differences in hemoglobin (p=0.741 and 0.975 for the continuous and discrete analyses, respectively).

Significant covariate effects included age (p=0.002 and p=0.004 for continuous and discrete analysis, respectively), race (p<0.001, continuous and discrete), occupation (p=0.002, continuous), lifetime cigarette smoking history (p<0.001, continuous and p=0.008, discrete), and current cigarette smoking history (p<0.001, continuous and discrete). There was a negative correlation with age (r=-0.063); the percent with abnormally low values increased from 3.8 percent and 3.7 percent in those born in or after 1942 and between 1923 and 1941, respectively, to 9.5 percent in those born in or before 1922. Blacks had a lower mean level (15.19 gm/dl) than nonblacks (15.70 gm/dl); the percent of Blacks with abnormally low levels was 13.9 percent compared to 3.3 percent in nonblacks. Officers had a lower mean level (15.57 gm/dl) than enlisted flyers (15.73 gm/dl) or enlisted groundcrew (15.73 gm/dl). Hemoglobin levels increased with both lifetime cigarette smoking history (r=0.070) and current cigarette smoking (r=0.247); in particular, the percentage of individuals with abnormally high levels increased with increased smoking (0.5%, 0.8%, and 2.4% for nonsmokers, at most 10 pack-year smokers, and greater than 10 pack-year smokers, respectively; 0.5%, 0.7%, 1.8%, and 4.6% for nonsmokers, former smokers, at most 20 cigarettes per day current smokers, and greater than 20 cigarettes per day current smokers, respectively).

The Ranch Hand and Comparison group means adjusted for covariates were not significantly different (p=0.810). Significant covariate effects included current cigarette smoking (p<0.001), and age-by-race, race-by-occupation, and race-by-current cigarette smoking history interactions (p=0.008, p=0.004, and p=0.050, respectively).

Adjusted discrete analyses detected statistically significant age-by-occupation (p=0.012) and race (p<0.001) effects, but no significant group difference (p=0.938).

Hematocrit

There were no statistically significant differences in hematocrit between the groups (p=0.850 and 0.999) for the unadjusted continuous and discrete analyses, respectively.

Significant covariates were age (p=0.013, continuous), race (p=0.002 and p<0.001, continuous and discrete analyses, respectively), occupation (p<0.001,

continuous), and lifetime and current cigarette smoking ($p<0.001$, continuous, for both variables). Hematocrit was negatively associated with age ($r=-0.052$). Blacks had a lower mean level (44.36%) than nonblacks (45.24%), and a much higher percent of Blacks than nonblacks had abnormally low values (7.3% vs. 1.7%). Officers had a lower mean level than enlisted flyers or enlisted groundcrew (44.82%, 45.43%, and 45.41%, respectively). Hematocrit levels were positively correlated with lifetime and current cigarette smoking ($r=0.087$ and $r=0.265$, respectively).

Adjusted continuous analyses detected a number of statistically significant covariate effects (current cigarette smoking, $p<0.001$; an age-by-race interaction, $p=0.007$; a race-by-occupation interaction, $p=0.011$; and a race-by-lifetime cigarette smoking history interaction, $p=0.040$), but the adjusted group means were not significantly different ($p=0.662$). Similarly, in the adjusted discrete analysis there were significant age ($p=0.022$) and race ($p<0.001$) effects, but no significant group effect ($p=0.920$).

MCV

There were no significant differences in MCV, either in the means ($p=0.151$) or percent with abnormal values ($p=0.766$), between the Ranch Hand and Comparison groups on unadjusted analysis.

Significant covariate effects included age ($p<0.001$, continuous and $p=0.002$, discrete), race ($p<0.001$ for both continuous and discrete analysis), occupation ($p<0.001$, continuous), and lifetime and current cigarette smoking ($p<0.001$ for all four pairwise associations). MCV was positively correlated with age ($r=0.139$) and the percentage of individuals with abnormally high values increased with age (7.5% for those born in or after 1942, 12.5% for those born between 1923 and 1941, and 15.5% for those born in or before 1922). Blacks had a lower mean and a greater percentage with abnormally low values than nonblacks (88.57 vs. 91.63 cubic micra; 10.2% vs. 0.6% with abnormally low values). Officers and enlisted flyers had similar mean levels, but enlisted groundcrew had a slightly lower mean level (91.87, 92.03, and 90.87 cubic micra, respectively). There was a positive association between MCV and lifetime and current cigarette smoking ($r=0.164$ and $r=0.216$, respectively), with increasing percentages of individuals with abnormally high MCV as smoking levels increased (3.0%, 11.1%, and 14.8% for nonsmokers, at most 10 pack-year smokers, and greater than 10 pack-year smokers, respectively; 3.0%, 8.4%, 17.7%, and 21.0% for nonsmokers, former smokers, at most 20 cigarettes per day current smokers, and greater than 20 cigarettes per day current smokers, respectively).

Adjusted group means were not significantly different ($p=0.342$). There were five statistically significant interactions (none involving group): age-by-race ($p=0.002$), age-by-lifetime cigarette smoking history ($p=0.015$), race-by-lifetime cigarette smoking history ($p=0.050$), occupation-by-current cigarette smoking ($p=0.002$), and lifetime cigarette smoking history-by-current cigarette smoking ($p<0.001$). Adjusted discrete analyses detected significant effects of age ($p=0.002$), race ($p<0.001$), and lifetime cigarette smoking history ($p<0.001$), but the adjusted relative risks were similar to the unadjusted relative risks and not statistically significant ($p=0.757$ overall).

MCH

The analyses of MCH mirrored those of MCV. The unadjusted mean levels did not differ significantly between the Ranch Hand and Comparison groups ($p=0.150$) and both groups had similar percentages of individuals with abnormal values ($p=0.882$).

Significant covariate effects were age ($p<0.001$, continuous and $p=0.002$, discrete), race ($p<0.001$ for both the continuous and discrete analyses), occupation ($p<0.001$, continuous and $p=0.037$, discrete), and lifetime and current cigarette smoking ($p<0.001$ for all four pairwise associations). MCH was positively correlated with age ($r=0.117$), and the percentage of individuals with abnormally high values increased with age (5.3% for those born in or after 1942, 9.7% for those born between 1923 and 1941, and 10.7% for those born in or before 1922). Blacks had a lower mean and a greater percentage with abnormally low values than nonblacks (30.38 vs. 31.82 micromicrograms; 5.1% vs. 0.3% with abnormally low values). Officers and enlisted flyers had similar mean values, but enlisted groundcrew had a slightly lower mean value (31.93, 31.89, and 31.51 micromicrograms, respectively). Correspondingly, the percent with abnormally high values was higher in the officers and enlisted flyers than in the enlisted groundcrew (9.1%, 9.4%, and 6.4%, respectively). There was a positive association between MCH and lifetime and current cigarette smoking ($r=0.136$ and $r=0.182$, respectively), with increasing percentages of individuals with abnormally high MCH as smoking levels increased (2.9%, 8.6%, and 10.6% for nonsmokers, at most 10 pack-year smokers, and greater than 10 pack-year smokers, respectively; 2.9%, 6.1%, 12.8%, and 15.8% for nonsmokers, former smokers, at most 20 cigarettes per day current smokers, and greater than 20 cigarettes per day current smokers, respectively).

Adjusted means and relative risks were similar to the unadjusted values and not significantly different between groups ($p=0.305$ and $p=0.780$ for the continuous and discrete analyses, respectively). In the continuous analysis, there were four statistically significant interactions, none involving group: age-by-race ($p=0.025$), age-by-lifetime cigarette smoking history ($p=0.021$), occupation-by-current cigarette smoking ($p=0.006$), and lifetime cigarette smoking history-by-current cigarette smoking ($p=0.002$). In the discrete analysis, the significant covariates were age, race, and lifetime cigarette smoking history (all at $p<0.001$).

MCHC

MCHC was similar in the two groups in unadjusted analyses ($p=0.715$ for the continuous analysis). There were no individuals in either group with abnormally low or abnormally high values. Discrete analyses were therefore not conducted on this variable.

Significant covariate effects in the continuous analysis included age ($p=0.013$), race ($p<0.001$), occupation ($p<0.001$), and lifetime and current cigarette smoking ($p<0.001$ in each case). MCHC was negatively correlated with age, lifetime cigarette smoking history, and current cigarette smoking, although the magnitudes of the respective correlation coefficients were exceedingly small ($r=-0.052$, $r=-0.077$, and $r=-0.080$, respectively). Blacks

had a slightly lower mean level than nonblacks (34.25 vs. 34.70 gm/dl), and officers had a slightly higher mean level than enlisted flyers or enlisted groundcrew (34.73, 34.63, and 34.65 gm/dl, respectively).

Adjusted group means were not significantly different (p=0.588); significant covariates in the general linear model were age (p<0.001), race (p<0.001), occupation (p=0.007), and current cigarette smoking (p<0.001).

Platelet Count

The Ranch Hand group had a significantly higher unadjusted mean platelet count than the Comparisons (265.47 vs. 259.62 thousand per cubic mm, p=0.017). Only four individuals in each group had abnormally low levels; thus, these individuals were pooled with those with normal levels in the discrete analyses. The estimated relative risk for abnormally high versus normal/abnormally low levels was also significant (Est. RR: 1.92, 95% C.I.: [1.08,3.41], p=0.027).

Significant covariates were age (p<0.001, continuous), occupation (p<0.001, continuous), lifetime cigarette smoking history (p<0.001, continuous and p=0.013, discrete), and current cigarette smoking (p<0.001, continuous). There was a slight negative correlation between platelet count and age (r=-0.086). Officers had a lower mean level than enlisted flyers who, in turn, had a lower mean level than enlisted groundcrew (256.16, 261.16, and 267.57 thousand per cubic mm, respectively). There was a slight positive correlation between platelet count and lifetime and current cigarette smoking (r=0.092 and r=0.097, respectively); the percentage of individuals with abnormally high values increased with pack-years of cigarette smoking (1.1%, 1.6%, and 3.1% for nonsmokers, at most 10 pack-year smokers, and greater than 10 pack-year smokers, respectively).

Mean platelet count values remained statistically significant in the adjusted analysis (adjusted means were 264.77 and 259.06 thousand per cubic mm in the Ranch Hand and Comparison groups, respectively; p=0.018). Significant covariates in the continuous analysis included occupation (p=0.035) and an age-by-lifetime cigarette smoking history interaction (p=0.050). None of the covariates was significant in the adjusted discrete analysis; the relative risk, therefore, remained significant at the same level as in the unadjusted analysis (p=0.027).

Exposure Index Analysis

The mean levels and frequency distributions for each hematologic variable at each level of the exposure index (low, medium, and high) and associated unadjusted tests within the Ranch Hand group are presented in Table 16-5. Separate analyses were performed within each occupational cohort (see Chapter 8). "M vs. L" and "H vs. L" represent the contrasts for medium versus low exposure and high versus low exposure, respectively. For each of these contrasts, the risks for abnormally low versus normal and abnormally high versus normal outcomes are generally given, unless pooling was required because of small cell sizes (as indicated).

TABLE 16-5.

Unadjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	Low vs. Normal		High vs. Normal	
			Low	Medium	High			Est. Relative Risk (95% C.I.)	p-Value	Est. Relative Risk (95% C.I.)	p-Value
RBC	Officer	n	130	124	123	Overall	0.971				
		Mean	4.887	4.883	4.894	M vs. L	0.938	—	—	—	—
		95% C.I.	(4.831, 4.943)	(4.824, 4.943)	(4.821, 4.967)	H vs. L	0.871	—	—	—	—
		Number/%									
		Abn. Low	4 3.1%	5 4.0%	7 5.7%	Overall	0.526[c]				
		Normal	125 96.2%	119 96.0%	114 92.7%	M vs. L		1.31 (0.34,5.00)	0.950	—	0.999
		Abn. High	1 0.8%	0 0.0%	2 1.6%	H vs. L		1.92 (0.55,6.71)	0.468	2.19 (0.20,24.51)	0.938
	Enlisted Flyer	n	55	63	53	Overall	0.416				
		Mean	4.857	4.879	4.947	M vs. L	0.749	—	—	—	—
		95% C.I.	(4.744, 4.971)	(4.800, 4.958)	(4.853, 5.040)	H vs. L	0.206	—	—	—	—
		Number/%									
		Abn. Low	2 3.6%	2 3.2%	1 1.9%	Overall	0.728[c]				
		Normal	53 96.4%	60 95.2%	52 98.1%	M vs. L		0.88 (0.12,6.49)	0.999	—	0.999
		Abn. High	0 0.0%	1 1.6%	0 0.0%	H vs. L		0.51 (0.04,5.78)	0.999	—	—
	Enlisted Groundcrew	n	147	158	140	Overall	0.547				
		Mean	4.998	5.024	4.972	M vs. L	0.591	—	—	—	—
		95% C.I.	(4.935, 5.062)	(4.958, 5.089)	(4.904, 5.039)	H vs. L	0.577	—	—	—	—
		Number/%									
		Abn. Low	4 2.7%	6 3.8%	6 4.3%	Overall	0.902[c]				
		Normal	141 95.9%	151 95.6%	133 95.0%	M vs. L		1.40 (0.39,5.08)	0.850	0.47 (0.04,5.21)	0.954
		Abn. High	2 1.4%	1 0.6%	1 0.7%	H vs. L		1.59 (0.44,5.75)	0.698	0.53 (0.05,5.91)	0.999

TABLE 16-5. (continued)

Unadjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	p-Value	Low vs. Normal: Est. Relative Risk (95% C.I.)	Low vs. Normal: p-Value	High vs. Normal: Est. Relative Risk (95% C.I.)	High vs. Normal: p-Value
WBC	Officer	n	130	124	123	Overall	0.406				
		Mean*	6.292	6.568	6.559	M vs. L	0.239	—	—	—	—
		95% C.I.*	(5.985, 6.614)	(6.248, 6.904)	(6.224, 6.911)	H vs. L	0.255	—	—	—	—
		Number/%									
		Abn. Low	11 8.5%	5 4.0%	10 8.1%	Overall	0.432				
		Normal	114 87.7%	112 90.3%	104 84.5%	M vs. L		0.46 (0.16,1.37)	0.246	1.42 (0.44,4.62)	0.768
		Abn. High	5 3.8%	7 5.6%	9 7.3%	H vs. L		1.00 (0.41,2.44)	0.999	1.97 (0.64,6.08)	0.354
	Enlisted Flyer	n	55	62	53	Overall	0.166				
		Mean*	7.584	7.047	6.846	M vs. L	0.173	—	—	—	—
		95% C.I.*	(6.972, 8.249)	(6.631, 7.490)	(6.302, 7.436)	H vs. L	0.068	—	—	—	—
		Number/%									
		Abn. Low	2 3.6%	0 0.0%	4 7.6%	Overall	0.126[c]				
		Normal	48 87.3%	60 96.8%	47 88.7%	M vs. L		—	0.408	0.32 (0.06,1.72)	0.320
		Abn. High	5 9.1%	2 3.2%	2 3.8%	H vs. L		2.04 (0.36,11.63)	0.696	0.41 (0.08,2.21)	0.504
	Enlisted Groundcrew	n	147	158	140	Overall	0.660				
		Mean*	7.011	7.170	7.215	M vs. L	0.488	—	—	—	—
		95% C.I.*	(6.679, 7.360)	(6.869, 7.484)	(6.901, 7.543)	H vs. L	0.390	—	—	—	—
		Number/%									
		Abn. Low	12 8.2%	6 3.8%	5 3.6%	Overall	0.327				
		Normal	127 86.4%	146 92.4%	128 91.4%	M vs. L		0.43 (0.16,1.19)	0.156	0.65 (0.22,1.92)	0.614
		Abn. High	8 5.4%	6 3.8%	7 5.0%	H vs. L		0.41 (0.14,1.21)	0.156	0.87 (0.31,2.46)	0.999

TABLE 16-5. (continued)

Unadjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	Low vs. Normal		High vs. Normal	
			Low	Medium	High			Est. Relative Risk (95% C.I.)	p-Value	Est. Relative Risk (95% C.I.)	p-Value
Hemoglobin	Officer	n	130	124	123	Overall	0.709				
		Mean	15.568	15.566	15.665	M vs. L	0.986	—	—	—	—
		95% C.I.	(15.392, 15.745)	(15.390, 15.743)	(15.457, 15.873)	H vs. L	0.474	—	—	—	—
		Number/%									
		Abn. Low	5 3.8%	3 2.4%	9 7.3%	Overall	0.455[c]				
		Normal	123 94.6%	119 96.0%	112 91.1%	M vs. L		0.62 (0.14,2.65)	0.776	0.97 (0.13,6.99)	0.999
		Abn. High	2 1.5%	2 1.6%	2 1.6%	H vs. L		1.98 (0.64,6.06)	0.350	0.91 (0.13,6.58)	0.999
	Enlisted Flyer	n	55	63	53	Overall	0.531				
		Mean	15.593	15.621	15.845	M vs. L	0.906	—	—	—	—
		95% C.I.	(15.168, 16.018)	(15.359, 15.883)	(15.540, 16.150)	H vs. L	0.308	—	—	—	—
		Number/%									
		Abn. Low	3 5.4%	2 3.2%	1 1.9%	Overall	0.522[c]				
		Normal	52 94.6%	60 95.2%	50 94.3%	M vs. L		0.58 (0.09,3.60)	0.886	—	0.999
		Abn. High	0 0.0%	1 1.6%	2 3.8%	H vs. L		0.35 (0.03,3.45)	0.676	—	0.496
	Enlisted Groundcrew	n	147	158	140	Overall	0.662				
		Mean	15.676	15.752	15.799	M vs. L	0.568	—	—	—	—
		95% C.I.	(15.483, 15.868)	(15.556, 15.948)	(15.628, 15.970)	H vs. L	0.370	—	—	—	—
		Number/%									
		Abn. Low	5 3.4%	8 5.1%	4 2.9%	Overall	0.145[c]				
		Normal	142 96.6%	149 94.3%	132 94.3%	M vs. L		1.52 (0.49,4.76)	0.660	—	0.999
		Abn. High	0 0.0%	1 0.6%	4 2.9%	H vs. L		0.86 (0.23,3.28)	0.999	—	0.112

TABLE 16-5. (continued)

Unadjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	p-Value	Low vs. Normal/High: Est. Relative Risk (95% C.I.)	Low vs. Normal/High: p-Value
Hematocrit	Officer	n	130	124	123	Overall	0.675		
		Mean	44.854	44.856	45.157	M vs. L	0.995	—	—
		95% C.I.	(44.371, 45.337)	(44.350, 45.363)	(44.529, 45.785)	H vs. L	0.437	—	—
		Number/%							
		Abn. Low	1 0.8%	0 0.0%	5 4.1%	Overall[a,c]	0.025		
		Normal	129 99.2%	123 99.2%	117 95.1%	M vs. L		—	0.999
		Abn. High	0 0.0%	1 0.8%	1 0.8%	H vs. L		5.46 (0.63,47.62)	0.188
	Enlisted Flyer	n	55	63	53	Overall	0.426		
		Mean	45.067	44.887	45.757	M vs. L	0.793	—	—
		95% C.I.	(43.837, 46.298)	(44.130, 45.645)	(44.882, 46.632)	H vs. L	0.335	—	—
		Number/%							
		Abn. Low	2 3.6%	1 1.6%	1 1.9%	Overall[a,c]	0.739		
		Normal	53 96.4%	62 98.4%	51 96.2%	M vs. L		0.43 (0.04,4.85)	0.898
		Abn. High	0 0.0%	0 0.0%	1 1.9%	H vs. L		0.51 (0.04,5.78)	0.999
	Enlisted Groundcrew	n	147	158	140	Overall	0.469		
		Mean	45.169	45.402	45.656	M vs. L	0.543	—	—
		95% C.I.	(44.622, 45.717)	(44.851, 45.954)	(45.147, 46.164)	H vs. L	0.219	—	—
		Number/%							
		Abn. Low	4 2.7%	5 3.2%	1 0.7%	Overall[a,c]	0.328		
		Normal	143 97.3%	153 96.8%	138 98.6%	M vs. L		1.17 (0.31,4.44)	0.999
		Abn. High	0 0.0%	0 0.0%	1 0.7%	H vs. L		0.26 (0.03,2.33)	0.402

TABLE 16-5. (continued)

Unadjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	Low vs. Normal		High vs. Normal	
			Low	Medium	High			Est. Relative Risk (95% C.I.)	p-Value	Est. Relative Risk (95% C.I.)	p-Value
MCV	Officer	n	130	124	123	Overall	0.650				
		Mean	91.853	91.936	92.337	M vs. L	0.881	—	—	—	—
		95% C.I.	(91.056, 92.650)	(91.177, 92.694)	(91.590, 93.084)	H vs. L	0.383	—	—	—	—
		Number/%									
		Abn. Low	1 0.8%	2 1.6%	1 0.8%	Overall	0.951[c]				
		Normal	117 90.0%	109 87.9%	109 88.6%	M vs. L		2.15 (0.19,23.81)	0.954	1.16 (0.51,2.66)	0.882
		Abn. High	12 9.2%	13 10.5%	13 10.6%	H vs. L		1.07 (0.07,17.24)	0.999	1.16 (0.51,2.66)	0.882
	Enlisted Flyer	n	55	63	53	Overall	0.742				
		Mean	92.711	92.011	92.517	M vs. L	0.459	—	—	—	—
		95% C.I.	(90.623, 94.459)	(90.932, 93.090)	(91.438, 93.596)	H vs. L	0.844	—	—	—	—
		Number/%									
		Abn. Low	1 1.8%	0 0.0%	0 0.0%	Overall	0.290[c]				
		Normal	44 80.0%	55 87.3%	49 92.4%	M vs. L		—	0.900	0.64 (0.23,1.76)	0.538
		Abn. High	10 18.2%	8 12.7%	4 7.6%	H vs. L		—	0.958	0.36 (0.10,1.23)	0.160
	Enlisted Groundcrew	n	147	158	140	Overall	0.015				
		Mean	90.441	90.490	92.011	M vs. L	0.934	—	—	—	—
		95% C.I.	(89.617, 91.265)	(89.641, 91.340)	(91.174, 92.849)	H vs. L	0.011	—	—	—	—
		Number/%									
		Abn. Low	2 1.4%	4 2.5%	1 0.7%	Overall	0.562				
		Normal	132 89.8%	134 84.8%	122 87.1%	M vs. L		1.97 (0.35,10.99)	0.712	1.52 (0.72,3.17)	0.356
		Abn. High	13 8.8%	20 12.7%	17 12.1%	H vs. L		0.54 (0.05,6.02)	0.999	1.41 (0.66,3.03)	0.484

TABLE 16-5. (continued)

Unadjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index Low	Exposure Index Medium	Exposure Index High	Exposure Index Contrast	p-Value	Low vs. Normal Est. Relative Risk (95% C.I.)	Low vs. Normal p-Value	High vs. Normal Est. Relative Risk (95% C.I.)	High vs. Normal p-Value
MCH	Officer	n	130	124	123	Overall	0.694				
		Mean	31.895	31.926	32.060	M vs. L	0.881	—	—	—	—
		95% C.I.	(31.606, 32.184)	(31.648, 32.203)	(31.778, 32.342)	H vs. L	0.419	—	—	—	—
		Number/%									
		Abn. Low	1 0.8%	0 0.0%	0 0.0%	Overall	0.707[c]				
		Normal	119 91.5%	115 92.7%	112 91.1%	M vs. L		—	0.999	0.93 (0.36,2.38)	0.999
		Abn. High	10 7.7%	9 7.3%	11 8.9%	H vs. L		—	0.999	1.17 (0.48,2.86)	0.908
	Enlisted Flyer	n	55	63	53	Overall	0.994				
		Mean	32.080	32.046	32.058	M vs. L	0.917	—	—	—	—
		95% C.I.	(31.480, 32.680)	(31.678, 32.414)	(31.674, 32.443)	H vs. L	0.950	—	—	—	—
		Number/%									
		Abn. Low	1 1.8%	0 0.0%	0 0.0%	Overall	0.483[c]				
		Normal	49 89.1%	58 92.1%	51 96.2%	M vs. L		—	0.926	0.84 (0.23,3.09)	0.999
		Abn. High	5 9.1%	5 7.9%	2 3.8%	H vs. L		—	0.990	0.38 (0.07,2.08)	0.452
	Enlisted Groundcrew	n	147	158	140	Overall	0.060				
		Mean	31.407	31.404	31.874	M vs. L	0.989	—	—	—	—
		95% C.I.	(31.097, 31.717)	(31.088, 31.720)	(31.570, 32.178)	H vs. L	0.041	—	—	—	—
		Number/%									
		Abn. Low	1 0.7%	3 1.9%	1 0.7%	Overall	0.397				
		Normal	138 93.9%	141 89.2%	124 88.6%	M vs. L		2.93 (0.30,28.57)	0.650	1.71 (0.70,4.21)	0.336
		Abn. High	8 5.4%	14 8.9%	15 10.7%	H vs. L		1.11 (0.07,17.86)	0.999	2.09 (0.86,5.09)	0.152

TABLE 16-5. (continued)

Unadjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	p-Value	Low vs. Normal: Est. Relative Risk (95% C.I.)	Low vs. Normal: p-Value	High vs. Normal: Est. Relative Risk (95% C.I.)	High vs. Normal: p-Value
MCHC	Officer	n	130	124	123	Overall	0.996				
		Mean	34.698	34.704	34.698	M vs. L	0.936	—	—	—	—
		95% C.I.	(34.604, 34.793)	(34.607, 34.801)	(34.599, 34.798)	H vs. L	0.999	—	—	—	—
		Number/%									
		Abn. Low	0 0.0%	0 0.0%	0 0.0%	Overall	—				
		Normal	130 100.0%	124 100.0%	123 100.0%	M vs. L	—	—	—	—	—
		Abn. High	0 0.0%	0 0.0%	0 0.0%	H vs. L	—	—	—	—	—
	Enlisted Flyer	n	55	631	53	Overall	0.061				
		Mean	34.594	34.811	34.623	M vs. L	0.031	—	—	—	—
		95% C.I.	(34.437, 34.752)	(34.681, 34.941)	(34.490, 34.755)	H vs. L	0.787	—	—	—	—
		Number/%									
		Abn. Low	0 0.0%	0 0.0%	0 0.0%	Overall	—				
		Normal	55 100.0%	63 100.0%	53 100.0%	M vs. L	—	—	—	—	—
		Abn. High	0 0.0%	0 0.0%	0 0.0%	H vs. L	—	—	—	—	—
	Enlisted Groundcrew	n	147	158	140	Overall	0.439				
		Mean	34.697	34.676	34.612	M vs. L	0.750	—	—	—	—
		95% C.I.	(34.603, 34.791)	(34.582, 34.770)	(34.519, 34.706)	H vs. L	0.217	—	—	—	—
		Number/%									
		Abn. Low	0 0.0%	0 0.0%	0 0.0%	Overall	—				
		Normal	147 100.0%	158 100.0%	140 100.0%	M vs. L	—	—	—	—	—
		Abn. High	0 0.0%	0 0.0%	0 0.0%	H vs. L	—	—	—	—	—

TABLE 16-5. (continued)

Unadjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index: Low	Exposure Index: Medium	Exposure Index: High	Exposure Index Contrast	p-Value	High vs. Normal/Low: Est. Relative Risk (95% C.I.)	p-Value
Platelet Count	Officer	n	130	124	122	Overall	0.230		
		Mean	250.12	261.57	260.51	M vs. L	0.122	—	—
		95% C.I.	(239.78, 260.45)	(251.46, 271.68)	(250.03, 270.98)	H vs. L	0.162	—	—
		Number/%							
		Abn. Low	2 1.5%	0 0.0%	0 0.0%	Overall[b,c]	0.473		
		Normal	126 96.9%	120 96.8%	117 95.9%	M vs. L		2.13 (0.38,11.86)	0.640
		Abn. High	2 1.5%	4 3.2%	5 4.1%	H vs. L		2.74 (0.52,14.37)	0.396
	Enlisted Flyer	n	55	63	53	Overall	0.217		
		Mean	277.31	271.75	257.09	M vs. L	0.626	—	—
		95% C.I.	(255.06, 299.56)	(262.05, 281.44)	(242.01, 272.18)	H vs. L	0.091	—	—
		Number/%							
		Abn. Low	1 1.8%	0 0.0%	0 0.0%	Overall[b,c]	0.046		
		Normal	49 89.1%	63 100.0%	51 96.2%	M vs. L		—	0.040
		Abn. High	5 9.1%	0 0.0%	2 3.8%	H vs. L		0.39 (0.07,2.12)	0.468
	Enlisted Groundcrew	n	147	158	140	Overall	0.506		
		Mean	269.54	275.34	267.80	M vs. L	0.390	—	—
		95% C.I.	(259.53, 279.53)	(266.02, 284.65)	(258.81, 276.79)	H vs. L	0.802	—	—
		Number/%							
		Abn. Low	1 0.7%	0 0.0%	0 0.0%	Overall[b,c]	0.013		
		Normal	142 96.6%	153 96.8%	138 98.6%	M vs. L		1.17 (0.31,4.44)	0.999
		Abn. High	4 2.7%	5 3.2%	2 1.4%	H vs. L		0.52 (0.09,2.87)	0.730

[a]High pooled with normal.
[b]Low pooled with normal.
[c]Small cell sizes may affect validity of p-value.
*Transformed from natural logarithm scale.
—Estimated relative risk not applicable for continuous analysis of a variable; estimated relative risk/confidence interval not given due to cells with zero frequency.

The results of adjusted exposure index analyses are presented in Table 16-6. Covariates examined included age, race, lifetime cigarette smoking history, and current cigarette smoking (only lifetime cigarette smoking history was used in the discrete analyses). On certain occasions, when data were sparse, fewer terms were retained in the final model.

The final interpretation of these exposure index data must await the reanalysis of the clinical data using the results of the serum dioxin assay. The report is expected in 1991.

Laboratory Examination Variables

RBC

No statistically significant differences overall, nor statistically significant subset contrasts, were found in either the continuous or discrete unadjusted analyses of RBC for any of the occupational cohorts.

In the adjusted analyses, there were no statistically significant exposure level effects in the officers or enlisted groundcrew, but there was a statistically significant exposure index-by-age interaction ($p=0.029$) in the continuous analysis of the enlisted flyers. The interaction is explored in Appendix M, Table M-2, where results are given stratified by age. The adjusted means increased slightly with exposure level in the cohort born between 1923 and 1941, but did not show such a trend in the subgroup born in or after 1942 (only two individuals were from the oldest age group). None of the p-values from the within-stratum contrasts was significant, however. Adjusted means, confidence intervals, and p-values are also presented after deleting this term from the model; no significant group difference was evident from that analysis.

WBC

There were no statistically significant differences in the continuous or discrete group comparisons for WBC, either unadjusted or adjusted for covariates.

Hemoglobin

The mean hemoglobin concentrations were not significantly different across the three exposure level categories for any of the occupational strata in unadjusted analyses. There were no significant unadjusted differences in the discrete analysis for officers, enlisted flyers, or enlisted groundcrew.

There was no significant difference in the adjusted continuous analysis for the officers, but there was a highly significant ($p=0.003$) exposure index-by-age interaction in the enlisted flyers and a significant ($p=0.012$) exposure index-by-lifetime cigarette smoking history interaction in the enlisted groundcrew. These interactions are explored in Appendix M, Table M-2. After stratifying by age for the enlisted flyers, there was no significant

TABLE 16-6.

Adjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	Low vs. Normal/High	
			Low	Medium	High			Adj. Relative Risk (95% C.I.)	p-Value
RBC	Officer	n	130	124	123	Overall	0.915		
		Adj. Mean	4.852	4.866	4.870	M vs. L	0.755	—	—
		95% C.I.	(4.707, 4.997)	(4.724, 5.008)	(4.726, 5.014)	H vs. L	0.688	—	—
		n	130	124	123	Overall[a]	0.665		
						M vs. L[a]		0.93 (0.28,3.07)	0.901
						H vs. L[a]		1.48 (0.48,4.61)	0.496
	Enlisted Flyer	n	55	63	53	Overall	0.211**		
		Adj. Mean**	4.971	4.977	5.080	M vs. L	0.935**	—	—
		95% C.I.**	(4.815, 5.127)	(4.835, 5.119)	(4.928, 5.232)	H vs. L	0.120**	—	—
		n	55	63	53	Overall[a]	0.871		
						M vs. L[a]		0.69 (0.15,3.24)	0.637
						H vs. L[a]		0.69 (0.13,3.60)	0.635
	Enlisted Groundcrew	n	147	158	140	Overall	0.734		
		Adj. Mean	5.032	5.048	5.010	M vs. L	0.742	—	—
		95% C.I.	(4.949, 5.115)	(4.964, 5.132)	(4.924, 5.096)	H vs. L	0.646	—	—
		n	147	158	140	Overall[a]	0.691		
						M vs. L[a]		1.65 (0.52,5.29)	0.398
						H vs. L[a]		1.34 (0.42,4.27)	0.616

TABLE 16-6. (continued)

Adjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	Low vs. Normal		High vs. Normal	
			Low	Medium	High			Adj. Relative Risk (95% C.I.)	p-Value	Adj. Relative Risk (95% C.I.)	p-Value
WBC	Officer	n	130	124	123	Overall	0.452				
		Adj. Mean[b]	5.568	5.795	5.720	M vs. L	0.217	—	—	—	—
		95% C.I.[b]	(5.031, 6.162)	(5.248, 6.399)	(5.172, 6.326)	H vs. L	0.404	—	—	—	—
		n	130	124	123	Overall	0.544				
						M vs. L		0.56 (0.20,1.53)	0.257	1.11 (0.38,3.25)	0.846
						H vs. L		1.23 (0.50,3.06)	0.654	1.46 (0.52,4.11)	0.471
	Enlisted Flyer	n	55	62	53	Overall	0.595				
		Adj. Mean[b]	6.855	6.586	6.600	M vs. L	0.355	—	—	—	—
		95% C.I.[b]	(6.197, 7.583)	(6.007, 7.222)	(5.983, 7.279)	H vs. L	0.403	—	—	—	—
		n	55	62	53	Overall	0.192				
						M vs. L		—	—	0.36 (0.09,1.41)	0.143
						H vs. L		1.40 (0.33,5.87)	0.646	0.55 (0.14,2.11)	0.384
	Enlisted Groundcrew	n	147	158	140	Overall	0.485				
		Adj. Mean[b]	6.626	6.855	6.760	M vs. L	0.231	—	—	—	—
		95% C.I.[b]	(6.304, 6.964)	(6.518, 7.209)	(6.419, 7.119)	H vs. L	0.489	—	—	—	—
		n	147	158	140	Overall	0.493				
						M vs. L		0.46 (0.17,1.19)	0.109	0.68 (0.25,1.84)	0.448
						H vs. L		0.55 (0.20,1.50)	0.241	0.77 (0.30,2.02)	0.601

TABLE 16-6. (continued)

Adjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	Low vs. Normal		High vs. Normal	
			Low	Medium	High			Adj. Relative Risk (95% C.I.)	p-Value	Adj. Relative Risk (95% C.I.)	p-Value
Hemoglobin	Officer	n	130	124	123	Overall	0.720				
		Adj. Mean	15.361	15.396	15.465	M vs. L	0.789	—	—	—	—
		95% C.I.	(14.944, 15.778)	(14.986, 15.806)	(15.049, 15.881)	H vs. L	0.426	—	—	—	—
		n	130	124	123	Overall	0.465				
						M vs. L		0.69 (0.20,2.41)	0.562	0.81 (0.17,3.72)	0.782
						H vs. L		1.95 (0.67,5.68)	0.223	1.07 (0.23,4.96)	0.927
	Enlisted Flyer	n	55	63	53	Overall	****				
		Adj. Mean	****	****	****	M vs. L	****	—	—	—	—
		95% C.I.	****	****	****	H vs. L	****	—	—	—	—
		n	55	63	53	Overall	0.796				
						M vs. L		0.57 (0.13,2.46)	0.455	1.10 (0.15,8.03)	0.923
						H vs. L		0.57 (0.12,2.73)	0.484	2.13 (0.32,14.09)	0.435
	Enlisted Groundcrew	n	147	158	140	Overall	0.652**				
		Adj. Mean**	15.494	15.529	15.615	M vs. L	0.788**	—	—	—	—
		95% C.I.**	(15.264 15.724)	(15.297 15.761)	(15.376 15.854)	H vs. L	0.367**	—	—	—	—
		n	147	158	140	Overall	0.474				
						M vs. L		1.71 (0.59,4.96)	0.324	2.13 (0.31,14.62)	0.441
						H vs. L		0.91 (0.28,2.96)	0.878	3.45 (0.62,19.14)	0.157

TABLE 16-6. (continued)

Adjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	Low vs. Normal/High	
			Low	Medium	High			Adj. Relative Risk (95% C.I.)	p-Value
Hematocrit	Officer	n	130	124	123	Overall	0.728		
		Adj. Mean	44.525	44.592	44.811	M vs. L	0.858	—	—
		95% C.I.	(43.327, 45.723)	(43.420, 45.764)	(43.621, 46.001)	H vs. L	0.446	—	—
		n	130	124	123	Overall[a]	0.086		
						M vs. L		—	0.610
						H vs. L		3.32 (0.69,15.97)	0.134
	Enlisted Flyer	n	55	63	53	Overall	****		
		Adj. Mean	****	****	****	M vs. L	****	—	—
		95% C.I.	****	****	****	H vs. L	****	—	—
		n	55	63	53	Overall[a]	0.403		
						M vs. L		0.49 (0.09,2.69)	0.413
						H vs. L		0.64 (0.12,3.46)	0.607
	Enlisted Groundcrew	n	147	158	140	Overall	0.453**		
		Adj. Mean	44.911	45.071	45.389	M vs. L	0.671**	—	—
		95% C.I.	(44.247, 45.575)	(44.400, 45.742)	(44.698, 46.080)	H vs. L	0.215**	—	—
		n	147	158	140	Overall[a]	0.159		
						M vs. L		1.33 (0.40,4.43)	0.635
						H vs. L		0.48 (0.11,2.14)	0.334

TABLE 16-6. (continued)

Adjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	High vs. Normal/Low	
			Low	Medium	High			Adj. Relative Risk (95% C.I.)	p-Value
MCV	Officer	n	130	124	123	Overall	0.792		
		Adj. Mean	91.753	91.632	91.997	M vs. L	0.826	—	—
		95% C.I.	(90.022, 93.484)	(89.937, 93.327)	(90.277, 93.717)	H vs. L	0.653	—	—
		n	130	124	123	Overall[c]	0.938		
						M vs. L		0.88 (0.39,2.03)	0.770
						H vs. L		1.01 (0.44,2.30)	0.981
	Enlisted Flyer	n	55	63	53	Overall	0.800		
		Adj. Mean	90.917	90.616	91.242	M vs. L	0.746	—	—
		95% C.I.	(88.743, 93.091)	(88.636, 92.596)	(89.134, 93.350)	H vs. L	0.736	—	—
		n	55	63	53	Overall[c]	0.333		
						M vs. L		0.66 (0.25,1.74)	0.406
						H vs. L		0.45 (0.15,1.33)	0.148
	Enlisted Groundcrew	n	147	158	140	Overall	0.028		
		Adj. Mean	89.439	89.554	90.896	M vs. L	0.844	—	—
		95% C.I.	(88.403, 90.475)	(88.508, 90.600)	(89.817, 91.975)	H vs. L	0.016	—	—
		n	147	158	140	Overall[c]	0.486		
						M vs. L		1.55 (0.75,3.20)	0.234
						H vs. L		1.28 (0.61,2.67)	0.516

TABLE 16-6. (continued)

Adjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	High vs. Normal/Low	
			Low	Medium	High			Adj. Relative Risk (95% C.I.)	p-Value
MCH	Officer	n	130	124	123	Overall	0.811		
		Adj. Mean	31.670	31.658	31.777	M vs. L	0.957	—	—
		95% C.I.	(31.023, 32.317)	(31.024, 32.292)	(31.134, 32.420)	H vs. L	0.595	—	—
		n	130	124	123	Overall[c]	0.791		
						M vs. L		0.78 (0.32,1.93)	0.591
						H vs. L		1.04 (0.43,2.48)	0.932
	Enlisted Flyer	n	55	63	53	Overall	0.882		
		Adj. Mean	31.315	31.429	31.476	M vs. L	0.722	—	—
		95% C.I.	(30.566, 32.064)	(30.748, 32.110)	(30.750, 32.202)	H vs. L	0.628	—	—
		n	55	63	53	Overall[c]	0.623		
						M vs. L		0.81 (0.25,2.59)	0.721
						H vs. L		0.52 (0.14,2.00)	0.344
	Enlisted Groundcrew	n	147	158	140	Overall	0.078		
		Adj. Mean	30.885	30.872	31.314	M vs. L	0.948	—	—
		95% C.I.	(30.504, 31.266)	(30.487, 31.257)	(30.917, 31.711)	H vs. L	0.053	—	—
		n	147	158	140	Overall[c]	0.291		
						M vs. L		1.78 (0.76,4.20)	0.186
						H vs. L		1.81 (0.78,4.20)	0.168

TABLE 16-6. (continued)

Adjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value
			Low	Medium	High		
MCHC	Officer	n	130	124	123	Overall	0.856
		Adj. Mean	34.477	34.515	34.506	M vs. L	0.595
		95% C.I.	(34.256, 34.698)	(34.298, 34.732)	(34.286, 34.726)	H vs. L	0.682
	Enlisted Flyer	n	55	63	53	Overall	0.049
		Adj. Mean	34.430	34.660	34.463	M vs. L	0.024
		95% C.I.	(34.193, 34.667)	(34.444, 34.876)	(34.233, 34.693)	H vs. L	0.750
	Enlisted Groundcrew	n	147	158	140	Overall	0.413
		Adj. Mean	34.498	34.441	34.412	M vs. L	0.375
		95% C.I.	(34.384, 34.612)	(34.326, 34.556)	(34.293, 34.531)	H vs. L	0.194

TABLE 16-6. (continued)

Adjusted Exposure Index for Hematologic Variables by Occupation

Variable	Occupation	Statistic	Exposure Index			Exposure Index Contrast	p-Value	High vs. Normal/Low	
			Low	Medium	High			Adj. Relative Risk (95% C.I.)	p-Value
Platelet Count	Officer	n	130	124	122	Overall	0.227		
		Adj. Mean	250.26	262.24	260.16	M vs. L	0.108	—	—
		95% C.I.	(226.71, 273.81)	(239.18, 285.30)	(236.74, 283.58)	H vs. L	0.182	—	—
		n	130	124	122	Overall[c]	0.769		
						M vs. L		1.15 (0.29,4.57)	0.847
						H vs. L		1.59 (0.42,6.08)	0.500
	Enlisted Flyer	n	55	63	53	Overall	****		
		Adj. Mean	****	****	****	M vs. L	****	—	—
		95% C.I.	****	****	****	H vs. L	****	—	—
		n	55	63	53	Overall[c]	0.068		
						M vs. L		—	0.039
						H vs. L		0.44 (0.11,1.86)	0.267
	Enlisted Groundcrew	n	147	158	140	Overall	0.618		
		Adj. Mean	265.82	270.87	264.49	M vs. L	0.457	—	—
		95% C.I.	(253.83, 277.81)	(258.77, 282.97)	(252.01, 276.97)	H vs. L	0.849	—	—
		n	147	158	140	Overall[c]	0.586		
						M vs. L		1.27 (0.39,4.13)	0.687
						H vs. L		0.64 (0.17,2.47)	0.517

[a]High pooled with normal for discrete analyses.
[b]Transformed from natural logarithm scale.
[c]Low pooled with normal for discrete analyses.
**Exposure index-by-covariate interaction ($0.01<p\leq0.05$)—adjusted mean, confidence interval, and p-value derived from a model fitted after deletion of this interaction.
****Exposure index-by-covariate interaction ($p\leq0.01$)—adjusted mean, confidence interval, and p-value not presented.
—Adjusted relative risk not applicable for continuous analysis of a variable; relative risk/confidence interval not given due to cells with zero frequency.

difference in hemoglobin means in the exposure levels for those born between 1923 and 1941; whereas a significant difference (p=0.006) emerged in those born in or after 1942 (only two individuals were born in or before 1922). However, in the younger subgroup where the significant difference occurred, the means did not exhibit a dose-response relationship.

The enlisted groundcrew were stratified according to pack-years of lifetime cigarette smoking. No significant differences emerged within any of the strata. The adjusted means were not significantly different after deleting the interaction term from the model.

No significant differences emerged in the adjusted discrete analyses for hemoglobin.

Hematocrit

Unadjusted mean hematocrit levels did not differ significantly across the three exposure level categories for any occupational subgroup. In the officers, there was a significant difference (p=0.025) in the discrete analysis, with five officers (4.1%) in the high exposure category exhibiting abnormally low levels, compared to one officer (0.8%) in the low exposure category and none in the medium exposure category. This p-value should be interpreted with caution, however, since it is based on small cell sizes. There were no significant differences in the enlisted flyers or enlisted groundcrew.

In the adjusted analyses of the officer cohort, the adjusted means were again not significantly different and the adjusted discrete comparison no longer reached significance (p=0.086). Adjusted relative risks in the enlisted flyers and enlisted groundcrew were similar to the unadjusted; estimated relative risks were not significantly different from 1. In the continuous analyses, a highly significant exposure index-by-age interaction emerged in the enlisted flyers (p=0.002) and a significant exposure index-by-lifetime cigarette smoking history interaction emerged in the enlisted groundcrew (p=0.010). (These results parallel those for hemoglobin, a closely related variable.) These interactions are explored more fully in Appendix M, Table M-2. As was the case for hemoglobin, a significant result was obtained in the enlisted flyers born in or after 1942 (p=0.003), but the adjusted differences were not consistent with a dose-response relationship. No other significant difference emerged in the enlisted flyers or enlisted groundcrew. After deleting the interaction term from the model in the enlisted groundcrew, the adjusted means were not significantly different (see Table 16-6).

MCV

In unadjusted continuous analyses of MCV, there were no significant differences in the officers or enlisted flyers, but in the enlisted groundcrew there was a statistically significant difference in the mean values (p=0.015), with those in the high exposure group having a greater mean level (92.011 cubic micra) than those in the low or medium exposure groups (90.441 and 90.490 cubic micra, respectively). These differences are consistent with a dose-response relationship and remained significant in the adjusted analyses

(Adj. means: 89.439, 89.554, and 90.896 cubic micra in the low, medium, and high exposure index groups, respectively; p=0.028). The adjusted discrete analysis in enlisted groundcrew was not significant (p=0.486). The adjusted continuous and discrete analyses in the officers and enlisted flyers did not detect any statistically significant differences.

MCH

The results for MCH were similar to those for MCV, i.e., no significant differences, unadjusted or adjusted, in the officers and enlisted flyers, but a borderline significant (p=0.060) difference overall in the continuous unadjusted analysis of the enlisted groundcrew. The contrast between the high and low exposure level means was significant at p=0.041. In the adjusted continuous analyses, the overall p-value was slightly greater (p=0.078) and the high versus low contrast not quite significant (p=0.053).

MCHC

There were no abnormally low or abnormally high values for MCHC. The means were not significantly different in the officers or enlisted groundcrew, but there was a borderline significant result (p=0.061) in the enlisted flyers. This was not consistent with a dose-response relationship, however. The mean MCHC was greater in the medium exposure level category than in the low exposure level category (p=0.031), but the mean in the high exposure level category was not much different from that in the low category (p=0.787).

Similar results emerged from the adjusted analysis, where the overall MCHC means were similar in the officer and enlisted groundcrew strata. The adjusted means were significantly different in the enlisted flyers (p=0.049), but only the medium versus low and not the high versus low contrast was statistically significant (p=0.024 and p=0.750, respectively).

Platelet Count

In the unadjusted analyses of platelet counts, no statistically significant differences were detected in the officers or enlisted groundcrew. There was a statistically significant difference in the discrete analysis for the enlisted flyers (p=0.046), but this was based on small numbers with the highest percentage of abnormal values occurring in the low exposure category (9.1% abnormally high vs. 0.0% in the medium exposure category and 3.8% in the high exposure category).

In the adjusted analyses of platelet count there were again no statistically significant differences in the officers or enlisted groundcrew. The adjusted discrete analysis for enlisted flyers was borderline significant overall (p=0.068) with a p-value of 0.039 for the medium versus low contrast. The continuous analysis in the enlisted flyers detected a highly significant exposure index-by-race interaction (p=0.008) and a significant exposure index-by-current cigarette smoking interaction (p=0.014). Appendix M, Table M-2, gives the results of adjusted analyses in the enlisted flyers after stratification by race and current cigarette smoking. The number of Blacks within

each smoking stratum was too few for meaningful analysis. Among nonblack nonsmokers and nonblack former smokers, the adjusted mean platelet count level was highest in the medium exposure category and lowest in the low exposure category. In nonblack current smokers of no more than 20 cigarettes per day, the mean platelet count decreased with increasing exposure level; in nonblacks currently smoking more than 20 cigarettes per day, the mean platelet count was lowest in the medium exposure category and was similar in the low and high exposure level categories. None of these within-stratum differences reached statistical significance, and were not suggestive of a dose-response effect.

A summary of the exposure index-by-covariate interactions is presented in Table 16-7. All occurred in the enlisted flyers or enlisted groundcrew. In the enlisted flyers, interactions involving age occurred for RBC, hemoglobin, and hematocrit, and interactions involving race and current cigarette smoking were detected for platelet count. In the enlisted groundcrew, interactions involving lifetime cigarette smoking history were detected for hemoglobin and hematocrit.

TABLE 16-7.

Summary of Exposure Index-by-Covariate Interactions From Adjusted Analyses for Hematologic Variables

Variable	Occupation	Covariate	p-Value
RBC	Enlisted Flyer	Age	0.029
Hemoglobin	Enlisted Flyer	Age	0.003
Hemoglobin	Enlisted Groundcrew	Lifetime Cigarette Smoking History	0.012
Hematocrit	Enlisted Flyer	Age	0.002
Hematocrit	Enlisted Groundcrew	Lifetime Cigarette Smoking History	0.010
Platelet Count	Enlisted Flyer	Race	0.008
Platelet Count	Enlisted Flyer	Current Cigarette Smoking	0.014

Longitudinal Analysis

Three variables--MCV, MCH, and platelet count--were investigated by longitudinal analysis. The average change in these parameters in a cohort of participants completing both the 1982 Baseline and 1987 followup examinations was determined for each group (Ranch Hands and Comparisons) and these changes were compared by a two-sample t-test. Table 16-8 gives the mean values at each examination, as well as the p-value from the test of equality of the differences. The mean values for those individuals who also participated in the 1985 followup examination are included for reference purposes.

The changes from Baseline to the 1987 followup examination were not significantly different between the two groups for MCV (p=0.883) or MCH (p=0.166). For platelet count the values decreased in both groups, but the drop was significantly greater in the Ranch Hands than in the Comparisons (p=0.015).

TABLE 16-8.

Longitudinal Analysis of Selected Hematologic Variables: A Contrast of 1982 Baseline and 1987 Followup Examination Means

Variable	Examination	Group Means		p-Value (Equality of Differences)
		Ranch Hand	Comparison	
MCV	1982 Baseline	88.973	88.615	
	1985 Followup	92.616	92.365	0.883
	1987 Followup	91.610	91.280	
MCH	1982 Baseline	30.840	30.638	
	1985 Followup	31.559	31.444	0.166
	1987 Followup	31.788	31.667	
Platelet Count	1982 Baseline	277.701	266.241	
	1985 Followup	271.704	267.984	0.015
	1987 Followup	265.624	258.987	

Note: Statistics for MCV and MCH are based on 938 Ranch Hands and 1,105 Comparisons who participated in the 1982 Baseline and 1987 followup examinations. The p-value given is in reference to the hypothesis test involving 1982 Baseline and 1987 followup results. Summary statistics on 917 of these Ranch Hands and 1,087 of these Comparisons who also participated in the 1985 followup are included for reference purposes only. Corresponding sample sizes for platelet count are 937 Ranch Hands and 1,105 Comparisons for 1982 Baseline and 1987 followup examinations, and 915 Ranch Hands and 1,086 Comparisons for the 1985 followup.

DISCUSSION

The complete blood count is the most frequently ordered laboratory test in ambulatory medicine. As indices of the three peripheral blood cell lines (erythrocytes, leukocytes, and platelets) the eight variables examined in the current section 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 as well.

In contrast to most organ systems, in which disease is usually apparent based on the history and physical examination, particular emphasis is placed on the laboratory in the detection of hematologic disorders. As quantitative indices, MCV, MCH, and MCHC can provide helpful insight into the morphologic classification of anemias.

The total white cell count is subject to variation 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 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 and numerous prescription and over-the-counter medications. The wide range of normal (130,000-400,000/cubic mm) is such that subtle changes in platelet survival could occur and not be identified as abnormal. Conversely, small differences in the total platelet count do not have a clinically significant effect on clotting mechanisms. Seven participants were found to have platelet counts greater than 500,000/cubic mm, with the highest count of 595,000/cubic mm. Detailed chart review failed to reveal any common diagnosis in this subgroup, and the similar distribution (four Ranch Hands, three Comparisons) weighs against the presence of a herbicide effect.

Analysis of the covariate-dependent variable data confirmed several expected clinical associations. In cigarette smokers, cellular hypoxia related to carboxyhemoglobin formation and systemic arterial desaturation in obstructive airway disease combine to raise the hemoglobin and hematocrit in comparison to nonsmokers. Less understood but recognized clinically is an elevation in the total white cell count, a finding that may relate to the increased incidence of chronic bronchitis in a nicotine dependent population.

While finding anemia should be considered abnormal at any age and should prompt appropriate medical evaluation, it is common to find a gradual decline in selected red cell indices with aging, an observation confirmed in the current study. Older participants were found to have statistically significant reductions in total red cell count and hemoglobin, associations that may reflect the increased incidence of chronic disease of multiple etiologies with advancing age. Several mechanisms have been suggested for the "anemia of chronic disorders," including a decreased red cell life span, diminished erythropoietin production, and impaired gastrointestinal absorption of iron.

The race-related associations can be explained on the basis of established clinical observations. In relation to nonblacks, Black participants had statistically significant reductions (or a higher percentage of individuals with abnormally low levels) in all red cell indices and in the total white cell count. In other studies, the mean hemoglobin level of Blacks averages 0.5 to 1.0 g/dl below that of nonblacks, a finding that may relate to the increased incidence of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and of hemoglobin variants (S and C) associated with heterozygous sickling disorders.

Blacks were found to have a greater incidence of abnormally low white cell counts than nonblacks (19% versus 6%). While the degree of leukopenia was slight and not likely of clinical significance, the cause of this finding is uncertain.

Of the eight laboratory variables examined, only two significant group differences were found. The Ranch Hands had a slightly higher (geometric) mean WBC count than the Comparisons. This small difference was not significant after covariate adjustment. Consistent with the Baseline and 1985 followup examinations, the Ranch Hands had a higher mean platelet count than the Comparisons and, in the present study, the difference has become statistically significant. The percentage of individuals with abnormally high platelet count values was also significantly greater in the Ranch Hands than in the Comparisons. Examination of the data from the three cycles shows that there has been a gradual reduction in platelet counts in both groups (although greater in the Ranch Hands) over time, suggesting an effect of age common to all participants. As a nonspecific reaction, the platelet count can be elevated in any occult disease process; this may be related to the slightly elevated erythrocyte sedimentation rate found in the Ranch Hands and reported in the General Health chapter. There is a highly significant association between sedimentation rate and platelet count, with 8.9 percent of those with abnormally high sedimentation rates exhibiting abnormally high platelet counts, compared to only 1.8 percent in those with normal sedimentation rates ($p<0.001$); the correlation between the (log) sedimentation rate and platelet count was also statistically significant ($r=0.156$, $p<0.001$). Whatever the cause, the difference in means of less than 10,000 per cubic mm is not clinically significant.

SUMMARY

The hematologic status of the Ranch Hand and Comparison groups was assessed by eight variables--RBC, WBC, hemoglobin, hematocrit, MCV, MCH, MCHC, and platelet count. Table 16-9 presents a summary of all of the unadjusted and adjusted group comparisons for these variables.

There were no unadjusted or adjusted statistically significant differences between groups for RBC. For WBC, there was a statistically significant difference between groups in the mean unadjusted (log) levels (geometric means in the Ranch Hand and Comparison groups were 6.875 and 6.703 thousand per cubic mm, respectively). The adjusted mean counts were not significantly different.

TABLE 16-9.

Overall Summary Results of Unadjusted and Adjusted Group Contrast Analyses of Hematologic Variables

Variable	Unadjusted		Adjusted		Direction of Results
	Discrete	Continuous	Discrete	Continuous	
RBC	NS	NS	NS	NS	
WBC	NS	0.038	NS	NS	RH>C
Hemoglobin	NS	NS	NS	NS	
Hematocrit	NS	NS	NS	NS	
MCV	NS	NS	NS	NS	
MCH	NS	NS	NS	NS	
MCHC	NS	NS	--	NS	
Platelet Count	0.035	0.017	0.035	0.018	RH>C, $RH^H > C^H$

--Analysis not performed (no abnormalities present).

NS: Not significant (p>0.10).

RH>C: Ranch Hand mean greater than Comparison mean.

$RH^H > C^H$: Ranch Hand percent abnormally high greater than Comparison percent abnormally high (p=0.027).

No statistically significant differences were detected in either the unadjusted or adjusted analyses of hemoglobin, hematocrit, MCV, MCH, and MCHC. For platelet count, the mean level was significantly greater in the Ranch Hands than in the Comparisons (265.47 vs. 259.62 thousand per cubic mm; p=0.017), and the percent of participants with elevated abnormally high values was also greater in the Ranch Hands than in the Comparisons (2.9% vs. 1.6%, Est. RR: 1.92, 95% C.I.: [1.08,3.41], p=0.027 [overall p-value = 0.035]). These differences remained statistically significant after adjustment for covariates (p=0.018 and p=0.035 for the continuous and overall discrete analyses, respectively). The elevation of platelets is not what one would expect based on the results of animal studies.[1]

Exposure index analyses in the Ranch Hand group did not detect any significant dose-response relationships or interactions in any of the

occupational cohorts (officers, enlisted flyers, enlisted groundcrew) for WBC or MCH. There was a statistically significant (p=0.029) exposure index-by-age interaction in the continuous analysis of RBC in the enlisted flyers. There were highly significant exposure index-by-age interactions in the continuous analysis of hemoglobin and hematocrit in the enlisted flyers (p=0.003 and p=0.002, respectively), as well as significant exposure index-by-lifetime cigarette smoking history interactions for these variables in the enlisted groundcrew (p=0.012 and p=0.010, respectively). Within each of the stratum, however, these results did not suggest a dose-response relationship. In the case of hematocrit, there was also a significant (p=0.025) exposure level effect in the unadjusted discrete analysis for the officers, with five individuals having abnormally low values in the high exposure index group, compared to one and none in the low and medium exposure level categories, respectively. This effect was of borderline significance after adjustment for covariates (p=0.086). For MCV, in the enlisted groundcrew, there was a significant difference in the mean values for the three exposure level categories, both unadjusted (p=0.015) and adjusted (p=0.028). These were consistent with a dose-response relationship. A significant difference in the adjusted means for MCHC emerged in the enlisted flyers (p=0.049). A significant difference was also detected for platelet count in the discrete analysis of the enlisted flyers (p=0.046). Continuous adjusted analyses of platelet count in the enlisted flyers detected a highly significant exposure index-by-race interaction (p=0.008) and a significant exposure index-by-current cigarette smoking interaction (p=0.014). The MCHC and platelet count findings did not generally support dose-response relationships.

Longitudinal analyses found no significant difference between the Ranch Hand and Comparison groups in the change in MCV and MCH from Baseline to the 1987 followup examination. However, the mean change in platelet count (a decrease) was significantly greater (p=0.015) in the Ranch Hand group than in the Comparison group.

In summary, there is little consistent evidence in this study to implicate an adverse effect of herbicide exposure on hematologic status. The Ranch Hands exhibited a slight, but statistically significant, increase in platelets, but data from animal studies suggest that TCDD exposure should cause a lowering of the platelet count, rather than an elevation.

CHAPTER 16

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CHAPTER 17

RENAL ASSESSMENT

INTRODUCTION

Background

Renal dysfunction and overt renal disease are not generally considered to be important clinical sequelae of exposure to phenoxy acids, chlorophenols, or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). However, renal failure due to acute intoxication from another phenoxy herbicide (MCPP) has been shown in two human cases, along with other severe toxic symptoms.[1]

In man and animals, 2,4-D, 2,4,5-T, and TCDD are excreted by the kidney, largely through a first-order kinetic process.[2-6] In most experimental animals, the kidney has been shown to contain only unmetabolized TCDD, while urine contains only metabolized TCDD compounds. Excretion of these compounds appears to be a function of the proximal convoluted tubules.[8-10] In experimental animals, renal damage is generally noted only when very high or lethal doses of TCDD have been administered, an observation that reflects the severe systemic toxicity of TCDD as contrasted to a doubtful role of primary nephrotoxicity.[11-14] In a number of experimental animals, the kidneys have been shown to be a site of TCDD deposition almost on the order of the liver in terms of the percentage of dose taken up per gram of tissue (adipose tissue shows the greatest uptake followed by liver, adrenals, and kidney).[7] It has been hypothesized that this high uptake rate may cause high exposures over prolonged times and lead to neoplastic growth or other damage.[15] Kidney-specific effects include an increase in retinyl esters in rats (which may be a response to TCDD-induced vitamin A deficiency), lipid peroxidation with low doses in some species of mice, enlarged kidneys in mink, and a high specificity for renal cytosol binding in hamsters.[15-18]

A variety of experimental pharmacokinetic studies have been conducted in man using both ingested 2,4-D and 2,4-5-T.[4-6,19,20] Most of these studies suggested an unconjugated excretion of these compounds by first-order kinetics. No acute deleterious renal effects, as detected by urinalysis or blood chemistries, were either noted or recorded for the volunteer subjects.

In contrast, following significant exposure to a horse arena filled with TCDD-contaminated waste products, a 6-year-old girl developed hemorrhagic cystitis, pyelonephritis, and proteinuria.[21] Horses exposed to this arena and other contaminated arenas also frequently manifested hematuria. A thorough 5-year followup examination of the girl was essentially normal and did not reveal any renal sequelae.[22]

Most dioxin morbidity studies have only briefly mentioned renal disease and function, and then in the context of routine data collected at physical examination rather than as a specific clinical focus. Some studies of significant occupational exposure have been almost devoid of commentary on renal dysfunction.[23-25] A contemporary study of a residentially exposed cohort showed negative renal findings.[26]

A Times Beach, Missouri, study demonstrated historical "trends" of increased urinary tract disease by questionnaire, along with a compatible pattern of leukocyturia and hematuria manifest at physical examination, but none of the observations was statistically significant.[27] Published morbidity studies of Monsanto workers reported essentially negative urinalysis findings, although data were not presented.[28,29]

Baseline Summary Results

The 1982 Baseline examination assessed renal disease and function by questionnaire and basic laboratory testing.

Based on questionnaire information, the Ranch Hand group reported significantly more kidney disease than the Comparisons ($p=0.039$), but this finding was not substantiated by laboratory test results, even when all abnormalities were summed over the five tests of blood urea nitrogen, creatinine clearance, presence of occult blood, five or more urine white blood cells per high-power field, and the presence of urine protein. The Comparison group manifested a twofold increase in proteinuria ($p=0.055$). The distributions of creatinine clearance levels were similar for the two groups, as were the means of blood urea nitrogen, urine specific gravity, and urine white blood cell count. Difficulty in assessing the degree and significance of hidden noncompliance to the full 24-hour urine collection made the interpretation of the creatinine clearance test results somewhat problematic. Known noncompliance to urine collection was much more frequent ($p<0.001$) in the elderly participants. Of 18 herbicide exposure analyses, only 1 (enlisted flyer category) was statistically significant vis-a-vis a history of kidney disease, and it did not demonstrate a linear increase from low to high exposure.

The validity of the renal assessment was reinforced by the demonstrated effects of the covariates of age (born in or after 1942, born before 1942) and 2-hour postprandial glucose levels (<120 mg/dl, ≥ 120 mg/dl). Blood urea nitrogen increased with age and urine specific gravity decreased ($p<0.001$ for both), while an abnormally high postprandial glucose level indicative of diabetes was associated only with an increasing urine specific gravity, as expected.

Overall, the Baseline renal assessment suggested an excess of historical kidney disease in the Ranch Hand group that was not corroborated by laboratory urinalysis testing.

1985 Followup Study Summary Results

A historical assessment of kidney disease/kidney stones by a review-of-systems questionnaire showed no significant differences between the Ranch Hand and Comparison groups.

Current renal function was evaluated by five laboratory variables: urine protein, occult blood, urine white blood cell counts, blood urea nitrogen, and urine specific gravity. Invasive procedures were not used.

The unadjusted analysis of proteinuria showed no group differences but the adjusted analysis showed an interaction of group and diabetic class; appropriate stratified analyses revealed that the prevalence of proteinuria was lower in the Ranch Hands than in the Comparisons in the diabetic and impaired strata, but higher in the normal strata for the Ranch Hands. These results were in contrast to the Baseline findings, which showed a marginally significant proteinuria in the Comparison group ($p=0.055$), and overall, lower prevalence rates of proteinuria.

The unadjusted prevalence rates for hematuria were similar for both groups. Three significant interactions involving group membership and covariates precluded a direct adjusted comparison of the estimated prevalence rates. Covariate analyses indicated increased hematuria in Blacks and enlisted personnel. A series of stratified analyses found no statistical differences for the Black enlisted strata of both groups. The approximate tenfold increase in hematuria in both groups over that observed at Baseline, was most likely due to different laboratory techniques (reagent-strip testing vs. microscopic observation).

Similar results were found for leukocyturia, i.e., a nonsignificant unadjusted analysis, and a significant three-way interaction (group, age, race) in the adjusted analysis. Significant covariate effects were noted for diabetic class and occupation for nonblack participants, whereas age was a significant adjusting variable for Blacks. A significant group difference was found only for the younger, nonblack Ranch Hands. The overall results were consistent with the Baseline findings.

Blood urea nitrogen levels did not vary significantly by group based on the unadjusted analysis. Adjusted analyses showed significant covariate effects for age and occupation and interactions for group and race and for race and diabetic class. An analysis stratified by race revealed no significant group differences for nonblacks, but a significantly higher adjusted mean blood urea nitrogen level in Black Comparisons than in Black Ranch Hands. Overall, the blood urea nitrogen results were similar to those observed at the Baseline examination.

Unadjusted urine specific gravity levels manifested marginally significant group differences ($p=0.082$). The adjusted analysis disclosed significant covariate effects of diabetic class and the interactions of group and race and group and occupation. Analyses by race showed no strata with significantly lower mean levels for Ranch Hands. In contrast to the Baseline values, the followup urine specific gravities were lower, a finding most likely attributable to differences in laboratory methodology (falling drop method vs. multistick procedure).

Exposure index analyses showed very little evidence of a dose-response relationship at the followup examination. No patterns in the relationship of prevalence rates or mean levels among the exposure index levels were seen within occupational strata.

The longitudinal analysis was based solely upon a contrast of blood urea nitrogen levels between the two examinations. The unadjusted mean blood urea nitrogen value increased slightly from the Baseline to the followup examination, but the increases were symmetrical in the two groups and non-significant.

In conclusion, none of the six renal assessment variables showed a significant difference between the Ranch Hand and Comparison groups by unadjusted tests. However, in the adjusted analyses, all renal measurements except reported kidney disease revealed group-by-covariate interactions. These interactions were often complex, making it impossible to reach a firm conclusion as to the presence of a group difference.

Parameters of the 1987 Renal Assessment

Dependent Variables

The 1987 renal assessment was based on questionnaire and laboratory data.

Questionnaire Data

In the self-administered family and personal history questionnaire, each study participant was asked whether they had ever experienced kidney trouble or kidney stones. A composite variable, history of kidney disease/stones, was constructed by assigning yes for any participant who responded with a yes to at least one of the two questions. This composite variable, based on self-reported and unverified information, was analyzed as a measure of the renal system function of each participant.

No participants were excluded for medical reasons from the analysis of this variable.

Laboratory Examination Data

Five renal variables were quantified by general laboratory procedures to assess nonspecific renal system function. The presence or absence of urine protein was determined by standard reagent strip testing. Hematuria and leukocyturia were measured by high-powered microscopic examination after centrifugation for 5 minutes. Blood urea nitrogen levels were assayed by a DuPont Automated Chemical Analyzer® model 500. Ames' Multisticks were used to measure urine specific gravity.

Urinary protein (absent/present), hematuria (absent/present), and leukocyturia ($\leq$2 white blood cells per high powered field [WBC/HPF] or >2 WBC/HPF) were analyzed as dichotomous variables. Blood urea nitrogen (mg/dl) and urine specific gravity were analyzed as continuous variables. A square root transformation was applied to the blood urea nitrogen data.

The cutpoint between abnormal and normal readings for blood urea nitrogen from Scripps Clinic and Research Foundation (SCRF) is 22 mg/dl, with readings above this value considered abnormal. The SCRF cutpoint for urine specific gravity is 1.005, with readings below this value considered abnormal. Statistical analyses dichotomizing these two variables were not performed.

No participants were excluded for medical reasons from the analysis of these variables.

Covariates

The effects of four covariates (age, race, occupation, and diabetic class) were examined in the analysis of renal data, both in pairwise associations with the dependent variables and in adjusted statistical analyses. Diabetic class was defined as diabetic (verified history of diabetes or $\geq$200 mg/dl glucose), impaired (140 mg/dl$\leq$glucose<200 mg/dl), and normal (<140 mg/dl glucose). Age was used in its continuous form for modeling purposes for all dependent variables; occasionally, age was trichotomized for presentation purposes (e.g., dependent variable-covariate associations and interaction summaries).

Relation to Baseline and 1985 Followup Studies

The six variables analyzed in the 1987 followup were analyzed in the Baseline and 1985 followup studies.

In the longitudinal analysis, changes in blood urea nitrogen from Baseline to the 1987 followup were assessed for group differences. This variable was selected because it was judged that serial blood urea nitrogen levels would be more indicative of long-term renal health than others. Furthermore, both examination measurements were made by the same brand and model of high-precision automated analyzer, permitting a more valid comparison.

Statistical Methods

The basic statistical analysis methods used in the analysis of the renal data are described in Chapter 7. Table 17-1 summarizes the statistical analyses performed for the 1987 assessment of the renal data. The first part of this table describes the dependent variables and identifies the candidate covariates and the statistical methods. The second part of the table provides additional information on the candidate covariates. Abbreviations are used extensively in the body of the table and are defined in footnotes.

Although no participants were excluded for medical reasons in the renal assessment as stated above, some dependent variable and covariate data were missing. The number of participants with missing data is provided in Table 17-2 by group and variable.

RESULTS

Ranch Hand and Comparison Group Contrast

The results of the unadjusted and adjusted Ranch Hand and Comparison group analyses are summarized in Tables 17-3 and 17-4, respectively. Table N-1 of Appendix N contains the dependent variable-covariate associations for the renal assessment. The summary of group-by-covariate interactions for group contrasts on the renal variables is provided in Table N-2 of Appendix N.