Table 15-19. Analysis of Absolute Lymphocytes (thousand/mm^3) (Continued)

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED

Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	1,211	1.75	1.75		
Background RH	381	1.75	1.77	0.02 --	0.671
Low RH	239	1.72	1.71	–0.04 --	0.383
High RH	239	1.79	1.78	0.03 --	0.575
Low plus High RH	478	1.75	1.74	–0.01 --	0.839

[a] Transformed from natural logarithm scale.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[d] P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED

Dioxin Category	n	Adj. Mean[a]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[b]	p-Value[c]
Comparison	1,210	1.79		
Background RH	380	1.83	0.04 --	0.356
Low RH	238	1.77	–0.02 --	0.572
High RH	239	1.77	–0.02 --	0.572
Low plus High RH	477	1.77	–0.02 --	0.457

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 15-19. Analysis of Absolute Lymphocytes (thousand/mm^3) (Continued)

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin +1)[b]		
1987 Dioxin	n	Mean[a]	R^2	Slope (Std. Error)[b]	p-Value
Low	288	1.71	0.002	0.009 (0.008)	0.239
Medium	287	1.76			
High	284	1.79			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of absolute lymphocytes versus log_2 (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)		
1987 Dioxin	n	Adj. Mean[a]	R^2	Adjusted Slope (Std. Error)[b]	p-Value
Low	287	1.73	0.050	0.007 (0.009)	0.455
Medium	286	1.79			
High	284	1.79			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of absolute lymphocytes versus log_2 (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

15.2.2.1.18 Absolute Monocytes

The Model 4 unadjusted analysis of absolute monocytes revealed a marginally significant positive association with 1987 dioxin levels (Table 15-20(g): p=0.059, slope=0.007). This association was nonsignificant after adjustment for covariates (Table 15-20(h): p=0.125). All analysis results from Models 1 through 3 also were nonsignificant (Table 15-20(a–f): p>0.10 for all other analyses).

Table 15-20. Analysis of Absolute Monocytes (thousand/mm^3)

(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED

Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***866***	***0.477***	***–0.004 --***	***0.648***
	Comparison	***1,249***	***0.481***		
Officer	Ranch Hand	341	0.463	–0.008 --	0.594
	Comparison	493	0.471		
Enlisted Flyer	Ranch Hand	151	0.470	–0.037 --	0.118
	Comparison	187	0.507		
Enlisted Groundcrew	Ranch Hand	374	0.492	0.011 --	0.455
	Comparison	569	0.482		

[a] Transformed from square root scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on square root scale.
[c] P-value is based on difference of means on square root scale.

(b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED

Occupational Category	Group	n	Adjusted Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***864***	***0.471***	***–0.006 --***	***0.544***
	Comparison	***1,248***	***0.476***		
Officer	Ranch Hand	340	0.461	–0.007 --	0.620
	Comparison	493	0.468		
Enlisted Flyer	Ranch Hand	151	0.452	–0.037 --	0.106
	Comparison	187	0.490		
Enlisted Groundcrew	Ranch Hand	373	0.489	0.008 --	0.590
	Comparison	568	0.481		

[a] Transformed from square root scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on square root scale.
[c] P-value is based on difference of means on square root scale.

Table 15-20. Analysis of Absolute Monocytes (thousand/mm^3) (Continued)

(c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED

Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	160	0.468	0.469	0.003	0.003 (0.006)	0.568
Medium	162	0.528	0.528			
High	156	0.472	0.470			

[a] Transformed from square root scale.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[c] Slope and standard error based on square root of absolute monocytes versus log_2 (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)		
Initial Dioxin	n	Adj. Mean[a]	R^2	Adj. Slope (Std. Error)[b]	p-Value
Low	159	0.463	0.041	0.000 (0.006)	0.999
Medium	162	0.508			
High	156	0.446			

[a] Transformed from square root scale.
[b] Slope and standard error based on square root of absolute monocytes versus log_2 (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED

Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	1,211	0.480	0.480		
Background RH	381	0.459	0.464	–0.016 --	0.221
Low RH	239	0.470	0.469	–0.011 --	0.480
High RH	239	0.508	0.502	0.022 --	0.136
Low plus High RH	478	0.489	0.486	0.006 --	0.606

[a] Transformed from square root scale.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on square root scale.
[d] P-value is based on difference of means on square root scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 15-20. Analysis of Absolute Monocytes (thousand/mm^3) (Continued)

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED

Dioxin Category	n	Adj. Mean[a]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[b]	p-Value[c]
Comparison	1,210	0.479		
Background RH	380	0.464	–0.015 --	0.223
Low RH	238	0.464	–0.015 --	0.319
High RH	239	0.499	0.020 --	0.193
Low plus High RH	477	0.482	0.003 --	0.822

[a] Transformed from square root scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on square root scale.
[c] P-value is based on difference of means on square root scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin +1)[b]		
1987 Dioxin	n	Mean[a]	R^2	Adjusted Slope (Std. Error)[b]	p-Value
Low	288	0.458	0.004	0.007 (0.004)	0.059
Medium	287	0.467			
High	284	0.503			

[a] Transformed from square root scale.
[b] Slope and standard error based on square root of absolute monocytes versus log_2 (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)		
1987 Dioxin	n	Adj. Mean[a]	R^2	Adjusted Slope (Std. Error)[b]	p-Value
Low	287	0.450	0.032	0.007 (0.004)	0.125
Medium	286	0.458			
High	284	0.493			

[a] Transformed from square root scale.
[b] Slope and standard error based on square root of absolute monocytes versus log_2 (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

15.2.2.1.19 Absolute Eosinophils (Nonzero Measurements)

For participants who had a positive number of absolute eosinophils, all analyses in Models 1 through 4 were nonsignificant (Table 15-21(a–h): p>0.10 for all analyses).

Table 15-21. Analysis of Absolute Eosinophils (thousand/mm^3) (Nonzero Measurements)

(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED

Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***760***	***0.159***	***–0.002 --***	***0.684***
	Comparison	***1,096***	***0.161***		
Officer	Ranch Hand	305	0.160	0.007 --	0.422
	Comparison	448	0.153		
Enlisted Flyer	Ranch Hand	134	0.162	–0.002 --	0.895
	Comparison	165	0.164		
Enlisted Groundcrew	Ranch Hand	321	0.157	–0.011 --	0.183
	Comparison	483	0.167		

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

(b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED

Occupational Category	Group	n	Adjusted Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***758***	***0.151***	***–0.003 --***	***0.576***
	Comparison	***1,095***	***0.154***		
Officer	Ranch Hand	304	0.154	0.007 --	0.347
	Comparison	448	0.147		
Enlisted Flyer	Ranch Hand	134	0.150	–0.003 --	0.806
	Comparison	165	0.153		
Enlisted Groundcrew	Ranch Hand	320	0.149	–0.013 --	0.106
	Comparison	482	0.162		

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

Table 15-21. Analysis of Absolute Eosinophils (thousand/mm^3) (Nonzero Measurements) (Continued)

(c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED

Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[a,b]	R^2	Slope (Std. Error)[c]	p-Value
Low	139	0.155	0.155	0.001	0.005 (0.025)	0.836
Medium	144	0.154	0.154			
High	134	0.157	0.157			

[a] Transformed from natural logarithm scale.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[c] Slope and standard error based on natural logarithm of absolute eosinophils versus log_2 (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)		
Initial Dioxin	n	Adj. Mean[a]	R^2	Adj. Slope (Std. Error)[b]	p-Value
Low	138	0.151	0.009	0.012 (0.029)	0.670
Medium	144	0.150			
High	134	0.155			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of absolute eosinophils versus log_2 (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 15-21. Analysis of Absolute Eosinophils (thousand/mm^3) (Nonzero Measurements) (Continued)

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED

Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	1,064	0.161	0.161		
Background RH	337	0.162	0.163	0.002 --	0.805
Low RH	206	0.156	0.155	–0.006 --	0.513
High RH	211	0.155	0.154	–0.007 --	0.434
Low plus High RH	417	0.155	0.155	–0.006 --	0.346

[a] Transformed from natural logarithm scale.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[d] P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED

Dioxin Category	n	Adj. Mean[a]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[b]	p-Value[c]
Comparison	1,063	0.153		
Background RH	336	0.156	0.003 --	0.677
Low RH	205	0.147	–0.006 --	0.447
High RH	211	0.144	–0.009 --	0.229
Low plus High RH	416	0.146	–0.007 --	0.194

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 15-21. Analysis of Absolute Eosinophils (thousand/mm³) (Nonzero Measurements) (Continued)

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin +1)[b]		
1987 Dioxin	n	Mean[a]	R^2	Slope (Std. Error)[b]	p-Value
Low	256	0.164	0.001	–0.017 (0.017)	0.330
Medium	250	0.156			
High	248	0.155			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of absolute eosinophils versus log_2 (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)		
1987 Dioxin	n	Adj. Mean[a]	R^2	Adjusted Slope (Std. Error)[b]	p-Value
Low	255	0.156	0.028	–0.010 (0.020)	0.608
Medium	249	0.149			
High	248	0.148			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of absolute eosinophils versus log_2 (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

15.2.2.1.20 Absolute Eosinophils (Zero versus Nonzero)

The percentage of participants with no absolute eosinophils present was not significantly associated with exposure group or dioxin in any of the Model 1 through 4 analyses (Table 15-22(a–h): p>0.37 for all analyses).

Table 15-22. Analysis of Absolute Eosinophils (Zero vs. Nonzero)

(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED

Occupational Category	Group	n	Number (%) Zero	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***866***	***106 (12.2)***	***1.00 (0.77,1.30)***	***0.995***
	Comparison	***1,249***	***153 (12.3)***		
Officer	Ranch Hand	341	36 (10.6)	1.18 (0.74,1.86)	0.493
	Comparison	493	45 (9.1)		
Enlisted Flyer	Ranch Hand	151	17 (11.3)	0.95 (0.49,1.86)	0.885
	Comparison	187	22 (11.8)		
Enlisted Groundcrew	Ranch Hand	374	53 (14.2)	0.93 (0.64,1.34)	0.689
	Comparison	569	86 (15.1)		

Table 15-22. Analysis of Absolute Eosinophils (Zero vs. Nonzero) (Continued)

(b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	*1.01 (0.77,1.31)*	*0.970*
Officer	1.18 (0.74,1.87)	0.489
Enlisted Flyer	0.95 (0.49,1.87)	0.893
Enlisted Groundcrew	0.92 (0.64,1.34)	0.674

(c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Number (%) Zero	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	160	21 (13.1)	0.95 (0.77,1.17)	0.630
Medium	162	18 (11.1)		
High	156	22 (14.1)		

[a] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED

Analysis Results for Log_2 (Initial Dioxin)		
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
477	0.92 (0.73,1.18)	0.521

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

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED

Dioxin Category	n	Number (%) Zero	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,211	147 (12.1)		
Background RH	381	44 (11.6)	0.96 (0.67,1.38)	0.833
Low RH	239	33 (13.8)	1.15 (0.77,1.73)	0.487
High RH	239	28 (11.7)	0.95 (0.61,1.46)	0.798
Low plus High RH	478	61 (12.8)	1.04 (0.76,1.44)	0.789

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 15-22. Analysis of Absolute Eosinophils (Zero vs. Nonzero) (Continued)

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED

Dioxin Category	n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
Comparison	1,210		
Background RH	380	1.07 (0.74,1.55)	0.705
Low RH	238	1.16 (0.77,1.76)	0.467
High RH	239	0.82 (0.53,1.27)	0.376
Low plus High RH	477	0.98 (0.71,1.35)	0.885

[a] Relative risk and confidence interval relative to Comparisons.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)	
1987 Dioxin	n	Number (%) Zero	Estimated Relative Risk (95% C.I.)[a]	p-Value
Low	288	32 (11.1)	1.05 (0.91,1.20)	0.528
Medium	287	37 (12.9)		
High	284	36 (12.7)		

[a] Relative risk for a twofold increase in 1987 dioxin.

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED

Analysis Results for Log_2 (1987 Dioxin + 1)		
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
857	0.99 (0.84,1.16)	0.894

[a] Relative risk for a twofold increase in 1987 dioxin.

15.2.2.1.21 Absolute Basophils (Nonzero Measurements)

For participants who had a positive number of absolute basophils, no significant relations were observed between basophils and exposure group or dioxin in Model 1 through 4 analyses (Table 15-23(a–h): p>0.18 for each analysis).

Table 15-23. Analysis of Absolute Basophils (thousand/mm^3) (Nonzero Measurements)

(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED

Occupational Category	Group	n	Mean[a]	Difference of Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***373***	***0.078***	***–0.002 --***	***0.315***
	Comparison	***580***	***0.080***		
Officer	Ranch Hand	149	0.076	–0.001 --	0.838
	Comparison	232	0.077		
Enlisted Flyer	Ranch Hand	75	0.079	–0.003 --	0.577
	Comparison	87	0.082		
Enlisted Groundcrew	Ranch Hand	149	0.079	–0.003 --	0.322
	Comparison	261	0.082		

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

(b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED

Occupational Category	Group	n	Adjusted Mean[a]	Difference of Adj. Means (95% C.I.)[b]	p-Value[c]
All	***Ranch Hand***	***372***	***0.072***	***–0.002 --***	***0.280***
	Comparison	***580***	***0.074***		
Officer	Ranch Hand	148	0.071	–0.001 --	0.669
	Comparison	232	0.073		
Enlisted Flyer	Ranch Hand	75	0.072	–0.002 --	0.682
	Comparison	87	0.074		
Enlisted Groundcrew	Ranch Hand	149	0.073	–0.003 --	0.326
	Comparison	261	0.076		

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

Table 15-23. Analysis of Absolute Basophils (thousand/mm^3) (Nonzero Measurements) (Continued)

(c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED

Initial Dioxin Category Summary Statistics				Analysis Results for Log_2 (Initial Dioxin)[b]		
Initial Dioxin	n	Mean[a]	Adj. Mean[ab]	R^2	Slope (Std. Error)[c]	p-Value
Low	62	0.077	0.078	0.013	0.009 (0.022)	0.685
Medium	58	0.075	0.076			
High	81	0.081	0.080			

[a] Transformed from natural logarithm scale.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[c] Slope and standard error based on natural logarithm of absolute basophils versus log_2 (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)		
Initial Dioxin	n	Adj. Mean[a]	R^2	Adj. Slope (Std. Error)[b]	p-Value
Low	61	0.073	0.082	–0.003 (0.026)	0.917
Medium	58	0.070			
High	81	0.073			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of absolute basophils versus log_2 (initial dioxin).

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED

Dioxin Category	n	Mean[a]	Adj. Mean[ab]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[c]	p-Value[d]
Comparison	562	0.080	0.080		
Background RH	168	0.077	0.078	–0.002 --	0.410
Low RH	92	0.076	0.076	–0.004 --	0.222
High RH	109	0.080	0.080	0.000 --	0.930
Low plus High RH	201	0.078	0.078	–0.002 --	0.482

[a] Transformed from natural logarithm scale.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[c] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[d] P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 15-23. Analysis of Absolute Basophils (thousand/mm³) (Nonzero Measurements) (Continued)

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED

Dioxin Category	n	Adj. Mean[a]	Difference of Adj. Mean vs. Comparisons (95% C.I.)[b]	p-Value[c]
Comparison	562	0.075		
Background RH	168	0.074	–0.001 --	0.657
Low RH	91	0.071	–0.004 --	0.183
High RH	109	0.073	–0.002 --	0.563
Low plus High RH	200	0.072	–0.003 --	0.220

[a] Transformed from natural logarithm scale.
[b] Difference of means after transformation to original scale; confidence interval on difference of means not presented because analysis was performed on natural logarithm scale.
[c] P-value is based on difference of means on natural logarithm scale.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin +1)[b]		
1987 Dioxin	n	Mean[a]	R^2	Slope (Std. Error)[b]	p-Value
Low	132	0.076	<0.001	0.006 (0.014)	0.674
Medium	109	0.079			
High	128	0.078			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of absolute basophils versus log_2 (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)		
1987 Dioxin	n	Adj. Mean[a]	R^2	Adjusted Slope (Std. Error)[b]	p-Value
Low	132	0.069	0.076	–0.006 (0.016)	0.716
Medium	108	0.072			
High	128	0.067			

[a] Transformed from natural logarithm scale.
[b] Slope and standard error based on natural logarithm of absolute basophils versus log_2 (1987 dioxin + 1).

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

15.2.2.1.22 Absolute Basophils (Zero versus Nonzero)

Unadjusted and adjusted Model 1 analyses of the percentage of participants with no absolute basophils revealed a significant difference between Ranch Hand and Comparison enlisted groundcrew (Table 15-24(a,b): p=0.068, Est. RR=1.28; p=0.065, Adj. RR=1.28, respectively). A greater percentage of

Ranch Hand than Comparison enlisted groundcrew had no absolute basophils. All other Model 1 contrasts were nonsignificant (Table 15-24(a,b): p>0.10 for each remaining contrast).

Table 15-24. Analysis of Absolute Basophils (Zero vs. Nonzero)

(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED

Occupational Category	Group	n	Number (%) Zero	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***866***	***493 (56.9)***	***1.15 (0.96,1.36)***	***0.126***
	Comparison	***1,249***	***669 (53.6)***		
Officer	Ranch Hand	341	192 (56.3)	1.15 (0.87,1.51)	0.338
	Comparison	493	261 (52.9)		
Enlisted Flyer	Ranch Hand	151	76 (50.3)	0.88 (0.57,1.35)	0.565
	Comparison	187	100 (53.5)		
Enlisted Groundcrew	Ranch Hand	374	225 (60.2)	1.28 (0.98,1.67)	0.068
	Comparison	569	308 (54.1)		

(b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	***1.16 (0.97,1.38)***	***0.106***
Officer	1.16 (0.88,1.53)	0.303
Enlisted Flyer	0.87 (0.57,1.34)	0.529
Enlisted Groundcrew	1.28 (0.98,1.68)	0.065

(c) MODEL 2: RANCH HANDS – INITIAL DIOXIN – UNADJUSTED

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Number (%) Zero	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	160	98 (61.3)	0.84 (0.73,0.97)	0.015
Medium	162	104 (64.2)		
High	156	75 (48.1)		

[a] Adjusted for percent body fat at the time of the blood measurement of dioxin.
[b] Relative risk for a twofold increase in initial dioxin.

Note: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Table 15-24. Analysis of Absolute Basophils (Zero vs. Nonzero) (Continued)

(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED

	Analysis Results for Log_2 (Initial Dioxin)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
477	0.81 (0.68,0.95)	0.012

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

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED

Dioxin Category	n	Number (%) Zero	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,211	649 (53.6)		
Background RH	381	213 (55.9)	1.09 (0.86,1.38)	0.459
Low RH	239	147 (61.5)	1.39 (1.04,1.84)	0.025
High RH	239	130 (54.4)	1.04 (0.78,1.37)	0.796
Low plus High RH	478	277 (58.0)	1.20 (0.97,1.49)	0.098

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED

Dioxin Category	n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
Comparison	1,210		
Background RH	380	1.11 (0.87,1.41)	0.395
Low RH	238	1.47 (1.10,1.95)	0.009
High RH	239	1.00 (0.75,1.33)	0.979
Low plus High RH	477	1.21 (0.97,1.50)	0.091

[a] Relative risk and confidence interval relative to Comparisons.

Note: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Table 15-24. Analysis of Absolute Basophils (Zero vs. Nonzero) (Continued)

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED

1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)	
1987 Dioxin	n	Number (%) Zero	Estimated Relative Risk (95% C.I.)[a]	p-Value
Low	288	156 (54.2)	0.97 (0.88,1.06)	0.496
Medium	287	178 (62.0)		
High	284	156 (54.9)		

[a] Relative risk for a twofold increase in 1987 dioxin.

Note: Low = ≤7.9 ppt; Medium = >7.9–19.6 ppt; High = >19.6 ppt.

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED

Analysis Results for Log_2 (1987 Dioxin + 1)		
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
857	0.94 (0.84,1.05)	0.257

[a] Relative risk for a twofold increase in 1987 dioxin.

Model 2 analyses displayed a significant association between initial dioxin and the percentage of participants with no absolute basophils, both with and without adjustment for covariates (Table 15-24(c,d): p=0.015, Est. RR=0.84; p=0.012, Adj. RR=0.81, respectively). As initial dioxin increased, the percentage of participants with no absolute basophils decreased.

A significant difference in the proportion of participants with no absolute basophils was observed between Ranch Hands in the low dioxin category and Comparisons in both Model 3 unadjusted and adjusted analyses (Table 15-24(e,f): p=0.025, Est. RR=1.39; p=0.009, Adj. RR=1.47, respectively). Also, the contrast of Comparisons with Ranch Hands in the low and high dioxin categories combined was marginally significant in both the unadjusted and adjusted analyses (Table 15-24(e,f): p=0.098, Est. RR=1.20; p=0.091, Adj. RR=1.21, respectively). Ranch Hands in these dioxin categories had a higher percentage of participants with no absolute basophils than did Comparisons. All other Model 3 contrasts, as well as the Model 4 analysis results, were nonsignificant (Table 15-24(e–h): p>0.25 for all analyses).

15.2.3 Longitudinal Analysis

Longitudinal analyses were conducted on platelet count to examine whether changes across time differed with respect to group membership (Model 1), initial dioxin (Model 2), and categorized dioxin (Model 3). Model 4 was not examined in longitudinal analyses because 1987 dioxin—the measure of exposure in these models—changes over time and is not available for all participants for 1982 or 1997.

Discrete and continuous analyses were performed for platelet count. The longitudinal analyses for these variables investigated the difference between the 1982 and 1997 examinations. These analyses were used to investigate the temporal effects of dioxin during the 15-year period between 1982 and 1997.

Participants who were abnormal in 1982 were not included in the longitudinal analysis of discrete dependent variables. The purpose of the longitudinal analysis was to examine the effects of dioxin exposure across time. Participants who were abnormal in 1982 were not considered to be at risk for developing the condition because the condition already existed at the time of the first collection of data for the AFHS (1982). Only participants considered normal at the 1982 examination were considered to be at risk for developing the condition; therefore, the rate of abnormalities under this restriction approximates an incidence rate between 1982 and 1997. That is, an incidence rate is a measure of the rate at which people without a condition develop the condition during a specified period of time (41). Summary statistics are provided for reference purposes for the 1985, 1987, and 1992 examinations.

The longitudinal analyses for platelet count in its discrete form examined relative risks at the 1997 examination for participants who were classified as normal at the 1982 examination. The adjusted relative risks estimated from each of the three models were used to investigate the change in the dependent variable over time. All three models were adjusted for age; Models 2 and 3 also were adjusted for the percentage of body fat at the time of the blood measurement of dioxin.

The longitudinal analysis for the platelet count in its continuous form examined the paired difference between the measurements from 1982 and 1997. These paired differences measured the change in platelet count over time. Each of the three models used in the longitudinal analysis was adjusted for age and platelet count as measured in 1982 (see Chapter 7, Statistical Methods). A square root transformation was applied to platelet count for analytic purposes.

15.2.3.1 Laboratory Variable

15.2.3.1.1 Platelet Count (Continuous)

A decrease was seen in both Ranch Hands and Comparison means between the baseline examination and the 1997 follow-up. The largest portion of the decrease was observed between 1992 and 1997. The change in platelet count means between 1982 and 1997 was examined for associations with group status and dioxin. In the Model 1 analysis, the change in platelet count means between 1982 and 1997 was significantly different between Ranch Hand and Comparison officers (Table 15-25(a): $p<0.001$). The difference was marginally significant in Ranch Hand and Comparison enlisted flyers (Table 15-25(a): $p=0.100$). For both occupations, Ranch Hands have decreased more than Comparisons over the 15-year time period. The difference was nonsignificant when Ranch Hands and Comparisons were examined across all occupations. No significant associations were observed between platelet count and dioxin in Model 2 (Table 15-25(b): $p=0.401$). In the Model 3 analysis, there was a marginally significant difference in the change in platelet count means between the background Ranch Hand dioxin category and Comparisons (Table 15-25(c)). The decrease in means between 1982 and 1997 was greater for Ranch Hands in the background dioxin category (66.0 thousand/mm^3) than for Comparisons (58.6 thousand/mm^3).

Table 15-25. Longitudinal Analysis of Platelet Count (thousand/mm^3) (Continuous)

(a) MODEL 1: RANCH HANDS VS. COMPARISONS

Occupational Category	Group	Mean[a]/(n) Examination 1982	1985	1987	1992	1997	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
All	***Ranch Hand***	***273.8***	***267.8***	***260.7***	***250.7***	***207.2***	***–66.6***	***–7.8***	***0.203***
		(807)	***(788)***	***(779)***	***(782)***	***(807)***			
	Comparison	***261.7***	***263.7***	***255.3***	***244.4***	***202.9***	***–58.8***		
		(966)	***(946)***	***(937)***	***(944)***	***(966)***			
Officer	Ranch Hand	262.4	258.3	252.0	239.3	196.9	–65.4	–13.5	<0.001
		(307)	(302)	(298)	(299)	(307)			
	Comparison	256.9	262.5	253.1	243.3	205.0	–51.9		
		(376)	(370)	(362)	(370)	(376)			
Enlisted Flyer	Ranch Hand	281.8	273.6	265.7	255.0	213.3	–68.5	–4.1	0.100
		(147)	(144)	(142)	(144)	(147)			
	Comparison	258.2	253.4	242.6	235.1	193.7	–64.4		
		(143)	(142)	(141)	(140)	(143)			
Enlisted Groundcrew	Ranch Hand	280.5	273.8	266.3	259.2	213.7	–66.7	–4.0	0.462
		(353)	(342)	(339)	(339)	(353)			
	Comparison	266.9	268.3	261.3	248.4	204.2	–62.7		
		(447)	(434)	(434)	(434)	(447)			

[a] Transformed from square root scale.
[b] Difference between 1997 and 1982 examination means after transformation to original scale.
[c] P-value is based on analysis of square root of platelet count; results adjusted for square root of platelet count in 1982 and age in 1997.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations.

Table 15-25. Longitudinal Analysis of Platelet Count (thousand/mm^3) (Continuous) (Continued)

(b) MODEL 2: RANCH HANDS – INITIAL DIOXIN

Initial Dioxin Category Summary Statistics						Analysis Results for Log_2 (Initial Dioxin)[b]	
	Mean[a]/(n) Examination						
Initial Dioxin	1982	1985	1987	1992	1997	Adjusted Slope (Std. Error)	p-Value
Low	266.5 (152)	265.1 (148)	257.6 (150)	247.0 (147)	204.0 (152)	0.039 (0.046)	0.401
Medium	277.4 (159)	268.2 (156)	262.8 (155)	252.9 (155)	208.0 (159)		
High	284.9 (147)	274.8 (144)	268.5 (142)	259.6 (144)	217.6 (147)		

[a] Transformed from square root scale.
[b] Results based on difference between square root of 1997 platelet count and square root of 1982 platelet count versus log_2 (initial dioxin); results adjusted for percent body fat at the date of the blood measurement of dioxin, square root of 1982 platelet count, and age in 1997.

Notes: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations.

Table 15-25. Longitudinal Analysis of Platelet Count (thousand/mm^3) (Continuous) (Continued)

(c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY

Dioxin Category	Mean[a]/(n) Examination 1982	1985	1987	1992	1997	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
Comparison	261.9 (938)	264.0 (921)	255.7 (911)	245.0 (917)	203.3 (938)	−58.6		
Background RH	270.3 (343)	265.2 (335)	257.5 (327)	247.4 (331)	204.3 (343)	−66.0	−7.4	0.071
Low RH	268.0 (228)	264.0 (221)	258.9 (223)	247.3 (220)	204.0 (228)	−64.0	−5.4	0.544
High RH	284.3 (230)	274.5 (227)	266.8 (224)	258.7 (226)	215.5 (230)	−68.8	−10.2	0.965
Low plus High RH	276.1 (458)	269.3 (448)	262.8 (447)	253.1 (446)	209.7 (458)	−66.4	−7.8	0.676

[a] Transformed from square root scale.
[b] Difference between 1997 and 1982 examination means after transformation to original scale.
[c] P-value is based on analysis of square root of 1997 platelet count; results adjusted for percent body fat at the date of the blood measurement of dioxin, square root of 1982 platelet count, and age in 1997.

Notes: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin > 10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin > 10 ppt, Initial Dioxin > 94 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations.

15.2.3.1.2 Platelet Count (Discrete)

The longitudinal analysis of 1997 platelet count in its discrete form was conditioned on participants who had a normal platelet count in 1982. In the Model 1 analyses, no significant difference was observed in the percentage of abnormally low platelet counts between Ranch Hands and Comparisons when all occupations were combined (Table 15-26(a1): p=0.681). Ranch Hand officers had a significantly higher percentage of abnormal low measurements than did Comparison officers (Table 15-26(a1): Adj. RR=2.71, p=0.046), and Ranch Hands enlisted flyers had a significantly smaller percentage of abnormal low measurements than did Comparison officers (Table 15-26(a1): Adj. RR=0.09, p=0.023). No significant differences were observed between Ranch Hands and Comparisons in the percentage of abnormally high measurements, although the sparse number of abnormally high measurements in 1997 precluded meaningful statistical analysis by occupation.

Table 15-26. Longitudinal Analysis of Platelet Count (Abnormal Low vs. Normal and Abnormal High vs. Normal)

(a1) MODEL 1: RANCH HANDS VS. COMPARISONS

Occupational Category	Group	Number (%) Abnormal Low/(n) Examination				
		1982	1985	1987	1992	1997
All	***Ranch Hand***	***2 (0.3)***	***1 (0.1)***	***0 (0.0)***	***3 (0.4)***	***21 (2.6)***
		807	***788***	***779***	***782***	***807***
	Comparison	***7 (0.7)***	***2 (0.2)***	***3 (0.3)***	***6 (0.6)***	***30 (3.1)***
		966	***946***	***937***	***944***	***966***
Officer	Ranch Hand	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.7)	14 (4.6)
		307	302	298	299	307
	Comparison	3 (0.8)	0 (0.0)	0 (0.0)	3 (0.8)	7 (1.9)
		376	370	362	370	376
Enlisted Flyer	Ranch Hand	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
		147	144	142	144	147
	Comparison	0 (0.0)	1 (0.7)	2 (1.4)	1 (0.7)	10 (7.0)
		143	142	141	140	143
Enlisted Groundcrew	Ranch Hand	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	6 (1.7)
		353	342	339	339	353
	Comparison	4 (0.9)	1 (0.2)	1 (0.2)	2 (0.5)	13 (2.9)
		447	434	434	434	447

Occupational Category	Group	Normal in 1982		Adj. Relative Risk (95% C.I.)[a]	p-Value[a]
		n in 1997	Number (%) Abnormal Low in 1997		
All	***Ranch Hand***	***799***	***20 (2.5)***	***0.88 (0.49,1.59)***	***0.681***
	Comparison	***950***	***27 (2.8)***		
Officer	Ranch Hand	305	13 (4.3)	2.71 (1.02,7.23)	0.046
	Comparison	372	6 (1.6)		
Enlisted Flyer	Ranch Hand	146	1 (0.7)	0.09 (0.01,0.71)	0.023
	Comparison	141	10 (7.1)		
Enlisted Groundcrew	Ranch Hand	348	6 (1.7)	0.71 (0.26,1.94)	0.501
	Comparison	437	11 (2.5)		

[a] Relative risk, confidence interval, and p-values are in reference to a contrast of 1982 and 1997 results; results adjusted for age in 1997.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations. Statistical analyses are based only on participants who had a normal platelet count in 1982 (see Chapter 7, Statistical Methods).

Table 15-26. Longitudinal Analysis of Platelet Count (Abnormal Low vs. Normal and Abnormal High vs. Normal) (Continued)

(a2) MODEL 1: RANCH HANDS VS. COMPARISONS

Occupational Category	Group	Number (%) Abnormal High/(n) Examination				
		1982	1985	1987	1992	1997
All	***Ranch Hand***	***6 (0.7)***	***12 (1.5)***	***16 (2.1)***	***9 (1.2)***	***4 (0.5)***
		807	***788***	***779***	***782***	***807***
	Comparison	***9 (0.9)***	***13 (1.4)***	***13 (1.4)***	***8 (0.9)***	***4 (0.4)***
		966	***946***	***937***	***944***	***966***
Officer	Ranch Hand	1 (0.3)	3 (1.0)	4 (1.3)	0 (0.0)	1 (0.3)
		307	302	298	299	307
	Comparison	1 (0.3)	3 (0.8)	5 (1.4)	3 (0.8)	3 (0.8)
		376	370	362	370	376
Enlisted Flyer	Ranch Hand	1 (0.7)	3 (2.1)	4 (2.8)	1 (0.7)	1 (0.7)
		147	144	142	144	147
	Comparison	2 (1.4)	3 (2.1)	1 (0.7)	2 (1.4)	1 (0.7)
		143	142	141	140	143
Enlisted Groundcrew	Ranch Hand	4 (1.1)	6 (1.8)	8 (2.4)	8 (2.4)	2 (0.6)
		353	342	339	339	353
	Comparison	6 (1.3)	7 (1.6)	7 (1.6)	3 (0.7)	0 (0.0)
		447	434	434	434	447

Occupational Category	Group	Normal in 1982		Adj. Relative Risk (95% C.I.)[a]	p-Value[a]
		n in 1997	Number (%) Abnormal High in 1997		
All	***Ranch Hand***	***799***	***3 (0.4)***	***1.81 (0.30,10.89)***	***0.516***
	Comparison	***950***	***2 (0.2)***		
Officer	Ranch Hand	305	1 (0.3)	--	0.999[b]
	Comparison	372	2 (0.5)		
Enlisted Flyer	Ranch Hand	146	1 (0.7)	--	0.999[b]
	Comparison	141	0 (0.0)		
Enlisted Groundcrew	Ranch Hand	348	1 (0.3)	--	0.912[b]
	Comparison	437	0 (0.0)		

[a] Relative risk, confidence interval, and p-values are in reference to a contrast of 1982 and 1997 results; results adjusted for age in 1997.

[b] P-value not presented because of the sparse number of participants with an abnormal high platelet count; results not adjusted for age in 1997.

--: Results not presented because of the sparse number of participants with an abnormal high platelet count.

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations. Statistical analyses are based only on participants who had a normal platelet count in 1982 (see Chapter 7, Statistical Methods).

Table 15-26. Longitudinal Analysis of Platelet Count (Abnormal Low vs. Normal and Abnormal High vs. Normal) (Continued)

(b1) MODEL 2: RANCH HANDS — INITIAL DIOXIN

Initial Dioxin	Number (%) Abnormal Low/(n) Examination				
	1982	1985	1987	1992	1997
Low	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	3 (2.0)
	152	148	150	147	152
Medium	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.5)
	159	156	155	155	159
High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
	147	144	142	144	147

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
	Normal in 1982			
Initial Dioxin	n in 1997	Number (%) Abnormal Low in 1997	Adj. Relative Risk (95% C.I.)[b]	p-Value
Low	150	2 (1.3)	0.83 (0.43,1.61)	0.586
Medium	158	4 (2.5)		
High	146	1 (0.7)		

[a] Adjusted for percent body fat at the time of the blood measurement of dioxin and age in 1997.
[b] Relative risk for a twofold increase in initial dioxin.

Notes: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations. Statistical analyses are based only on participants who had a normal platelet count in 1982 (see Chapter 7, Statistical Methods).

(b2) MODEL 2: RANCH HANDS — INITIAL DIOXIN

Initial Dioxin	Number (%) Abnormal High/(n) Examination				
	1982	1985	1987	1992	1997
Low	1 (0.7)	1 (0.7)	3 (2.0)	1 (0.7)	0 (0.0)
	152	148	150	147	152
Medium	1 (0.6)	2 (1.3)	4 (2.6)	3 (1.9)	1 (0.6)
	159	156	155	155	159
High	1 (0.7)	3 (2.1)	3 (2.1)	4 (2.8)	1 (0.7)
	147	144	142	144	147

Table 15-26. Longitudinal Analysis of Platelet Count (Abnormal Low vs. Normal and Abnormal High vs. Normal) (Continued)

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
	Normal in 1982			
Initial Dioxin	n in 1997	Number (%) Abnormal High in 1997	Adj. Relative Risk (95% C.I.)[b]	p-Value
Low	150	0 (0.0)	1.28 (0.32,5.19)	0.726
Medium	158	1 (0.6)		
High	146	0 (0.0)		

[a] Adjusted for percent body fat at the time of the blood measurement of dioxin and age in 1997.
[b] Relative risk for a twofold increase in initial dioxin.

Notes: Low = 27–63 ppt; Medium = >63–152 ppt; High = >152 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations. Statistical analyses are based only on participants who had a normal platelet count in 1982 (see Chapter 7, Statistical Methods).

(c1) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY

	Number (%) Abnormal Low/(n) Examination				
Dioxin Category	1982	1985	1987	1992	1997
Comparison	6 (0.6)	1 (0.1)	2 (0.2)	4 (0.4)	28 (3.0)
	938	921	911	917	938
Background RH	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.6)	12 (3.5)
	343	335	327	331	343
Low RH	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.5)	6 (2.6)
	228	221	223	220	228
High RH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
	230	227	224	226	230
Low plus High RH	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	8 (1.8)
	458	448	447	446	458

Table 15-26. Longitudinal Analysis of Platelet Count (Abnormal Low vs. Normal and Abnormal High vs. Normal) (Continued)

	Normal in 1982			
Dioxin Category	n in 1997	Number (%) Abnormal Low in 1997	Adj. Relative Risk (95% C.I.)[ab]	p-Value[b]
Comparison	923	26 (2.8)		
Background RH	339	12 (3.5)	1.33 (0.66,2.69)	0.424
Low RH	226	5 (2.2)	0.70 (0.26,1.85)	0.471
High RH	228	2 (0.9)	0.32 (0.07,1.36)	0.122
Low plus High RH	454	7 (1.5)	0.47 (0.19,1.18)	0.107

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin and age in 1997.

Notes: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin >10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin >10 ppt, Initial Dioxin > 94 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations. Statistical analyses are based only on participants who had a normal platelet count in 1982 (see Chapter 7, Statistical Methods).

(c2) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY

	Number (%) Abnormal High/(n) Examination				
Dioxin Category	1982	1985	1987	1992	1997
Comparison	9 (1.0)	13 (1.4)	13 (1.4)	8 (0.9)	4 (0.4)
	938	921	911	917	938
Background RH	3 (0.9)	5 (1.5)	6 (1.8)	1 (0.3)	2 (0.6)
	343	335	327	331	343
Low RH	1 (0.4)	2 (0.9)	4 (1.8)	2 (0.9)	0 (0.0)
	228	221	223	220	228
High RH	2 (0.9)	4 (1.8)	6 (2.7)	6 (2.7)	2 (0.9)
	230	227	224	226	230
Low plus High RH	3 (0.7)	6 (1.3)	10 (2.2)	8 (1.8)	2 (0.4)
	458	448	447	446	458

Table 15-26. Longitudinal Analysis of Platelet Count (Abnormal Low vs. Normal and Abnormal High vs. Normal) (Continued)

Dioxin Category	Normal in 1982			
	n in 1997	Number (%) Abnormal High in 1997	Adj. Relative Risk (95% C.I.)[ab]	p-Value[b]
Comparison	923	2 (0.2)		
Background RH	339	2 (0.6)	2.17 (0.30,15.65)	0.442
Low RH	226	0 (0.0)	--	0.999[c]
High RH	228	1 (0.4)	3.79 (0.32,45.31)	0.293
Low plus High RH	454	1 (0.2)	--	0.999[c]

[a] Relative risk and confidence interval relative to Comparisons.
[b] Adjusted for percent body fat at the time of the blood measurement of dioxin and age in 1997.
[c] P-value not presented because of the sparse number of participants with an abnormal high platelet count; results not adjusted for age in 1997.
--: Results not presented because of the sparse number of participants with an abnormal high platelet count.

Notes: RH = Ranch Hand.
Comparison: 1987 Dioxin ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin >10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin >10 ppt, Initial Dioxin > 94 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations. Statistical analyses are based only on participants who had a normal platelet count in 1982 (see Chapter 7, Statistical Methods).

Model 2 analyses did not show a significant association of initial dioxin with either abnormally low or abnormally high platelet counts (Table 15-26(b1) and (b2): $p>0.58$ for each analysis). The Model 3 analyses of categorized dioxin also did not show any significant associations with abnormal platelet count levels (Table 15-26(c1) and (c2): $p>0.10$ for all analyses).

15.3 DISCUSSION

As indices of the three peripheral blood lines—RBCs, WBCs, and platelets—the hematologic variables analyzed are widely used in clinical medicine and are relied upon heavily to reflect disease not only of the hematopoietic system, but in other organ systems as well. Although lacking specificity, abnormalities in the hemoglobin, hematocrit, and total WBC count often serve as a sensitive first alert to the presence of a host of infection, inflammatory, and neoplastic disease states across multiple organ systems and point to the need for further investigation.

As elements essential to normal coagulation, the platelets have a short half-life and are most subject to decreased survival in a wide range of diseases, toxic chemical exposures, and in the presence of numerous over-the-counter and prescription medications. The broad range of normal for the platelet count (130 thousand/mm^3 to 400 thousand/mm^3) is such that subtle changes in platelet survival can occur and not be identified as abnormal. Only extreme variations in the platelet count—less than 50 thousand/mm^3 and

greater than 800 thousand/mm^3—are associated with the classic complications of spontaneous bleeding or blood clot formation.

Similar to the 1987 and 1992 examinations, most of the significant results were limited to the platelet and WBC analyses. Ranch Hand enlisted flyers and groundcrew had higher mean platelet counts than Comparisons, but the differences in the means (14.9 thousand/mm^3 and 9.3 thousand/mm^3, respectively) cannot be considered biologically meaningful.

Few of the serum dioxin analyses yielded significant results. In a pattern consistent with a dose-response effect, a positive association was noted between the mean platelet count and initial dioxin levels in the low, medium, and high categories. When adjusted for covariates, the associations were no longer significant. Similarly, in the model using 1987 dioxin levels, Ranch Hands with the highest levels of serum dioxin had significantly higher mean platelet counts than did Comparisons, but after adjustment for covariates, the association was not significant. Once again, the difference in the means was relatively small (never more than 14 thousand/mm^3). In the discrete analyses, which can be considered more relevant clinically, no significant group or occupational differences were noted, nor was there any evidence for a dioxin effect.

In the 1987 examinations, the mean WBC and platelet counts and the erythrocyte sedimentation rates were higher in Ranch Hands than Comparisons, raising the possibility of a subclinical inflammatory response associated with prior dioxin exposure. In the current study as in 1992, no significant group differences were noted in any of these indices. The unadjusted analyses of the WBC and platelet variables and, as noted in Chapter 9, of erythrocyte sedimentation rate, have yielded results consistent with a subtle dose-response effect in relation to both initial and 1987 dioxin levels. After adjustment for covariates, none of the findings remained significant.

Dependent variable-covariate associations confirmed numerous observations that have been well-established in clinical practice. 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. The increased incidence of chronic bronchitis in smokers is often associated with an elevation in the total WBC count. Of participants smoking at least one pack per day, 16.1 percent had abnormally elevated WBC counts, versus a prevalence of 1.4 percent in nonsmokers ($p=0.001$). Older participants were found to have statistically significant reductions in the total RBC, hemoglobin, and hematocrit associations that may reflect the increased incidence of chronic disease associated with age.

Race-related associations were noted. When compared to non-Black participants, Black participants had statistically significant reductions in the RBC indices, findings 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 prevalence of abnormally low RBC counts than non-Blacks (7.8% vs. 4.6%), although the difference in the means (4.99 thousand/mm^3 vs. 4.95 thousand/mm^3) is not statistically significant and is not likely clinically meaningful.

The longitudinal analyses documented a reduction in the total platelet count in each group and across all occupational strata. As documented in the 1987 follow-up report, Ranch Hands continue to have a greater reduction in the total platelet count over time than do Comparisons, although the current means (207.2 thousand/mm^3 vs. 202.9 thousand/mm^3) are nearly equal.

In conclusion, analyses of 13 hematologic variables yielded no significant group differences between the Ranch Hand and Comparison cohorts, and these results are consistent with the 1992 follow-up examination. In those participants most heavily exposed, the slight increase in the platelet count referenced above may still reflect a subtle biologic effect of dioxin exposure. Apart from platelet count, there appears to be little evidence to support a relation between dioxin exposure and adverse effects to the hematopoietic system.

15.4 SUMMARY

The hematology assessment included analyses of 13 variables each from the laboratory examination. For each variable, associations with group (Model 1), initial dioxin (Model 2), categorized dioxin (Model 3), and 1987 dioxin (Model 4) were assessed. Continuous and discrete analyses were performed for each cell count variable as well as for prothrombin time. RBC morphology, as well as blood count variables, was also analyzed. In addition, due to the large number of nonzero measurements for absolute neutrophils (bands), absolute eosinophils, and absolute basophils, investigations on these variables consisted of two analyses. First, a discrete analysis was performed on the proportion of zero measurements, and second, a continuous analysis was performed on the nonzero measurements.

15.4.1 Model 1: Group Analysis

As shown in Table 15-27, in both the unadjusted and adjusted analyses of the cell count variables, only the analyses of platelet count revealed significant group differences. In the continuous analysis, group differences were significant for each occupation but not significant when examined across all occupations. The platelet count mean was higher for Comparison officers and higher for Ranch Hands in both enlisted flyers and enlisted groundcrew. In the discrete analysis of platelet count, unadjusted and adjusted results also revealed consistent results. Significant group differences in the percentage of abnormally low platelet counts were found within the officer and enlisted flyer strata. For officers, more Ranch Hands than Comparisons exhibited an abnormally low platelet count. Conversely, for enlisted flyers, more Comparisons than Ranch Hands had an abnormally low platelet count.

Table 15-27. Summary of Group Analysis (Model 1) for Hematology Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Laboratory				
Red Blood Cell (RBC) Count (C)	ns	ns	ns	NS
Red Blood Cell (RBC) Count (D)				
Abnormal Low vs. Normal	NS	ns	NS	ns
Abnormal High vs. Normal	ns	ns	NS	ns
White Blood Cell (WBC) Count (C)	NS	NS	ns	NS
White Blood Cell (WBC) Count (D)				
Abnormal Low vs. Normal	NS	NS	NS	NS
Abnormal High vs. Normal	NS	ns	NS	NS
Hemoglobin (C)	NS	ns	ns	NS
Hemoglobin (D)				
Abnormal Low vs. Normal	NS	NS	NS	ns
Abnormal High vs. Normal	ns	NS	NS	ns

Table 15-27. Summary of Group Analysis (Model 1) for Hematology Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	UNADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Hematocrit (C)	ns	ns	ns	NS
Hematocrit (D)				
Abnormal Low vs. Normal	NS	ns	NS	ns
Abnormal High vs. Normal	ns	ns	NS	ns
Platelet Count (C)	NS	–0.012	+0.005	+0.004
Platelet Count (D)				
Abnormal Low vs. Normal	ns	+0.021	–0.032	ns
Abnormal High vs. Normal	NS	ns	NS	NS
Prothrombin Time (C)	ns	NS	ns	ns
Prothrombin Time (D)	NS	NS	ns	NS
RBC Morphology (D)	NS	NS	NS	NS
Absolute Neutrophils (Segs) (C)	NS	ns	ns	NS
Absolute Neutrophils (Bands) (Nonzero Measurements) (C)	NS	NS	ns	NS*
Absolute Neutrophils (Bands) (Zero vs. Nonzero) (D)	ns	ns	+0.029	ns
Absolute Lymphocytes (C)	NS	NS	ns	NS
Absolute Monocytes (C)	ns	ns	ns	NS
Absolute Eosinophils (Nonzero Measurements) (C)	ns	NS	ns	ns
Absolute Eosinophils (Zero vs. Nonzero) (D)	NS	NS	ns	ns
Absolute Basophils (Nonzero Measurements) (C)	ns	ns	ns	ns
Absolute Basophils (Zero vs. Nonzero) (D)	NS	NS	ns	NS*

Note: NS*: Marginally significant ($0.05<p\leq0.10$).
NS or ns: Not significant ($p>0.10$).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥ 1.00 for discrete analysis; difference of means nonnegative for continuous analysis.
–: Relative risk <1.00 for discrete analysis; difference of means negative for continuous analysis.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 15-27. Summary of Group Analysis (Model 1) for Hematology Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	ADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Laboratory				
Red Blood Cell (RBC) Count (C)	ns	ns	ns	NS
Red Blood Cell (RBC) Count (D)				
Abnormal Low vs. Normal	NS	ns	NS	ns
Abnormal High vs. Normal	ns	ns	NS	ns
White Blood Cell (WBC) Count (C)	NS	NS	ns	NS
White Blood Cell (WBC) Count (D)				
Abnormal Low vs. Normal	NS	NS	NS	NS
Abnormal High vs. Normal	ns	ns	ns	ns
Hemoglobin (C)	ns	ns	ns	NS
Hemoglobin (D)				
Abnormal Low vs. Normal	NS	NS	NS	ns
Abnormal High vs. Normal	ns	NS	--	--
Hematocrit (C)	ns	ns	ns	NS
Hematocrit (D)				
Abnormal Low vs. Normal	NS	ns	NS	ns
Abnormal High vs. Normal	ns	--	--	--
Platelet Count (C)	NS	–0.014	+0.003	+0.011
Platelet Count (D)				
Abnormal Low vs. Normal	ns	+0.022	–0.029	ns
Abnormal High vs. Normal	NS	ns	NS	NS
Prothrombin Time (C)	ns	NS	ns	ns
Prothrombin Time (D)	NS	NS	--	NS
RBC Morphology (D)	NS	NS	NS	NS
Absolute Neutrophils (Segs) (C)	NS	ns	ns	NS
Absolute Neutrophils (Bands) (Nonzero Measurements) (C)	NS	NS	ns	NS*
Absolute Neutrophils (Bands) (Zero vs. Nonzero) (D)	ns	ns	+0.026	ns
Absolute Lymphocytes (C)	NS	NS	ns	ns
Absolute Monocytes (C)	ns	ns	ns	NS
Absolute Eosinophils (Nonzero Measurements) (C)	ns	NS	ns	ns
Absolute Eosinophils (Zero vs. Nonzero) (D)	NS	NS	ns	ns
Absolute Basophils (Nonzero Measurements) (C)	ns	ns	ns	ns
Absolute Basophils (Zero vs. Nonzero) (D)	NS	NS	ns	NS*

Note: NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
NS or ns: Not significant ($p>0.10$).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥1.00 for discrete analysis; difference of means nonnegative for continuous analysis.
–: Relative risk<1.00 for discrete analysis; difference of means negative for continuous analysis.
--: Analysis not performed because of the sparse number of participants with an abnormality.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

The unadjusted and adjusted results from the analyses of the blood count variables also were similar. The continuous analyses of absolute neutrophils (bands) revealed a marginally significant higher mean for Ranch Hands within the enlisted groundcrew stratum. A greater percentage of zero measurements were found among Ranch Hand enlisted flyers than among Comparison enlisted flyers. For the analysis of absolute basophils, the difference in the proportions of zero measurements was marginally significant and higher for Ranch Hands than for Comparisons within the enlisted groundcrew stratum.

15.4.2 Model 2: Initial Dioxin Analysis

Unadjusted analyses of the cell count variables revealed several significant associations with initial dioxin, as shown in Table 15-28. The continuous analyses of WBC count, hemoglobin, hematocrit, and platelet count each showed a significant, positive relation with initial dioxin. After adjustment for covariate information, each association was nonsignificant. Other significant results include the discrete unadjusted and adjusted analyses of WBC count, revealing a decrease in the proportion of abnormally low WBC counts as initial dioxin increased.

Table 15-28. Summary of Initial Dioxin Analysis (Model 2) for Hematology Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Laboratory		
Red Blood Cell (RBC) Count (C)	NS	ns
Red Blood Cell (RBC) Count (D)		
Abnormal Low vs. Normal	ns	ns
Abnormal High vs. Normal	ns	ns
White Blood Cell (WBC) Count (C)	+0.035	NS
White Blood Cell (WBC) Count (D)		
Abnormal Low vs. Normal	–0.012	–0.043
Abnormal High vs. Normal	ns	ns
Hemoglobin (C)	+0.023	NS
Hemoglobin (D)		
Abnormal Low vs. Normal	ns*	ns
Abnormal High vs. Normal	NS	NS
Hematocrit (C)	+0.021	NS
Hematocrit (D)		
Abnormal Low vs. Normal	ns	NS
Abnormal High vs. Normal	NS	NS
Platelet Count (C)	+0.012	NS
Platelet Count (D)		
Abnormal Low vs. Normal	ns	ns
Abnormal High vs. Normal	NS	ns
Prothrombin Time (C)	ns	NS
Prothrombin Time (D)	ns	ns
RBC Morphology	ns	NS
Absolute Neutrophils (Segs) (C)	NS	NS
Absolute Neutrophils (Bands) (Nonzero Measurements) (C)	ns	–0.040
Absolute Neutrophils (Bands) (Zero vs. Nonzero) (D)	ns	ns

Table 15-28. Summary of Initial Dioxin Analysis (Model 2) for Hematology Variables (Ranch Hands Only) (Continued)

Variable	Unadjusted	Adjusted
Absolute Lymphocytes (C)	NS*	NS*
Absolute Monocytes (C)	NS	NS
Absolute Eosinophils (Nonzero Measurements) (C)	NS	NS
Absolute Eosinophils (Zero vs. Nonzero) (D)	ns	ns
Absolute Basophils (Nonzero Measurements) (C)	NS	ns
Absolute Basophils (Zero vs. Nonzero) (D)	–0.015	–0.012

Note: NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥1.00 for discrete analysis.
–: Relative risk<1.00; slope negative for continuous analysis.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or slope nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

Among the blood count variables, the result from the unadjusted analysis of absolute neutrophils (bands) was nonsignificant. After adjustment for covariates, a significant negative association was revealed, where neutrophils decreased as initial dioxin increased. A marginally significant and positive association between initial dioxin and absolute lymphocyte count was found in both the unadjusted and adjusted analyses. In addition, a significant negative association between initial dioxin and the proportion of zero measurements was revealed in both the unadjusted and adjusted analyses of absolute basophils.

15.4.3 Model 3: Categorized Dioxin Analysis

Several contrasts that were marginally significant or significant in the unadjusted categorized dioxin analyses of the cell count variables and RBC morphology became nonsignificant or marginally significant in the adjusted analyses. A summary of the results of the categorized dioxin analysis is provided in Table 15-29. The contrast of Ranch Hands in the low dioxin category with Comparisons for RBC count was marginally significant without adjustment for covariates but nonsignificant after adjustment. When Ranch Hands in the high dioxin category were contrasted with Comparisons in the unadjusted, continuous analysis of WBC count, a significant difference was revealed. In the adjusted analysis the result was nonsignificant. The unadjusted contrast of Ranch Hands in the low dioxin category, with Comparisons in the discrete analysis of WBC count resulted in a significant difference, although the difference was marginally significant in the adjusted analysis. Continuous hemoglobin analysis revealed a marginally significant difference between Ranch Hands in the high category and Comparisons. In addition, analysis of RBC morphology revealed a marginally significant difference between Ranch Hands in the low dioxin category and Comparisons. After adjustment for covariates for both hemoglobin and RBC morphology, the results were nonsignificant. Except for the low Ranch Hand contrast for RBC count, each of the aforementioned contrasts displayed either a greater percentage of Ranch Hands with an abnormality or Ranch Hands with a higher cell count mean.

Table 15-29. Summary of Categorized Dioxin Analysis (Model 3) for Hematology Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Laboratory				
Red Blood Cell (RBC) Count (C)	ns	ns*	NS	ns
Red Blood Cell (RBC) Count (D)				
Abnormal Low vs. Normal	NS	NS	ns	ns
Abnormal High vs. Normal	ns	ns	ns	ns
White Blood Cell (WBC) Count (C)	ns	ns	+0.029	NS
White Blood Cell (WBC) Count (D)				
Abnormal Low vs. Normal	NS	+0.027	ns	NS
Abnormal High vs. Normal	ns	ns	NS	NS
Hemoglobin (C)	ns	ns	NS*	NS
Hemoglobin (D)				
Abnormal Low vs. Normal	NS	NS	ns	ns
Abnormal High vs. Normal	NS	ns	ns	ns
Hematocrit (C)	ns	ns	NS	NS
Hematocrit (D)				
Abnormal Low vs. Normal	ns	ns	ns	ns
Abnormal High vs. Normal	ns	ns	ns	ns
Platelet Count (C)	ns	ns	+<0.001	+0.017
Platelet Count (D)				
Abnormal Low vs. Normal	NS	ns	ns*	ns*
Abnormal High vs. Normal	NS	ns	NS	ns
Prothrombin Time (C)	NS	ns	ns	ns
Prothrombin Time (D)	NS	NS	ns	ns
RBC Morphology	NS	NS*	NS	NS
Absolute Neutrophils (Segs) (C)	ns	ns	+0.028	NS
Absolute Neutrophils (Bands) (Nonzero Measurements) (C)	NS	NS*	NS	+0.029
Absolute Neutrophils (Bands) (Zero vs. Nonzero) (D)	ns	NS	ns	ns
Absolute Lymphocytes (C)	NS	ns	NS	ns
Absolute Monocytes (C)	ns	ns	NS	NS
Absolute Eosinophils (Nonzero Measurements) (C)	NS	ns	ns	ns
Absolute Eosinophils (Zero vs. Nonzero) (D)	ns	NS	ns	NS
Absolute Basophils (Nonzero Measurements) (C)	ns	ns	NS	ns
Absolute Basophils (Zero vs. Nonzero) (D)	NS	+0.025	NS	NS*

Table 15-29. Summary of Categorized Dioxin Analysis (Model 3) for Hematology Variables (Ranch Hands vs. Comparisons) (Continued)

Note: NS or ns: Not significant (p>0.10).
NS* or ns*: Marginally significant (0.05<p≤0.10).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥1.00 for discrete analysis; difference of means nonnegative for continuous analysis.
--: Analysis not performed because of the sparse number of participants with an abnormality.

P-value given if p≤0.05.

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

	ADJUSTED			
Variable	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Laboratory				
Red Blood Cell (RBC) Count (C)	NS	ns	ns	ns
Red Blood Cell (RBC) Count (D)				
Abnormal Low vs. Normal	NS	ns	NS	ns
Abnormal High vs. Normal	ns	ns	NS	ns
White Blood Cell (WBC) Count (C)	NS	ns	NS	ns
White Blood Cell (WBC) Count (D)				
Abnormal Low vs. Normal	NS	NS*	ns	NS
Abnormal High vs. Normal	ns	ns	NS	ns
Hemoglobin (C)	ns	ns	NS	NS
Hemoglobin (D)				
Abnormal Low vs. Normal	NS	ns	ns	ns
Abnormal High vs. Normal	NS	--	ns	--
Hematocrit (C)	ns	ns	NS	ns
Hematocrit (D)				
Abnormal Low vs. Normal	NS	ns	NS	ns
Abnormal High vs. Normal	--	--	ns	--
Platelet Count (C)	ns	NS	+0.002	+0.038
Platelet Count (D)				
Abnormal Low vs. Normal	NS	ns	ns*	ns*
Abnormal High vs. Normal	ns	--	NS	--
Prothrombin Time (C)	NS	ns	ns	ns
Prothrombin Time (D)	NS	NS	ns	ns
RBC Morphology	NS	NS	NS	NS
Absolute Neutrophils (Segs) (C)	NS	ns	NS	NS
Absolute Neutrophils (Bands) (Nonzero Measurements) (C)	NS	NS*	NS	+0.038
Absolute Neutrophils (Bands) (Zero vs. Nonzero) (D)	NS	NS	ns	ns
Absolute Lymphocytes (C)	NS	ns	ns	ns
Absolute Monocytes (C)	ns	ns	NS	NS

Table 15-29. Summary of Categorized Dioxin Analysis (Model 3) for Hematology Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	ADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Absolute Eosinophils (Nonzero Measurements) (C)	NS	ns	ns	ns
Absolute Eosinophils (Zero vs. Nonzero) (D)	NS	NS	ns	ns
Absolute Basophils (Nonzero Measurements) (C)	ns	ns	ns	ns
Absolute Basophils (Zero vs. Nonzero) (D)	NS	+0.009	NS	NS*

Note: NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥1.00 for discrete analysis; difference of means nonnegative for continuous analysis.
--: Analysis not performed because of the sparse number of participants with an abnormality.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Results from the analyses of platelet count, both in the continuous and discrete forms, were consistent in the unadjusted and adjusted analyses. Significantly higher mean platelet counts were observed for Ranch Hands in the high and in the low and high dioxin categories combined than for Comparisons. The discrete analysis of platelet count revealed a marginally significant lower percentage of abnormally low platelet counts for Ranch Hands in the high and in the low and high dioxin categories combined than for Comparisons.

The analysis of the blood count variables revealed significant results for absolute neutrophils (segs) and absolute neutrophils (bands) in the continuous form and absolute basophils (zero versus nonzero measurements). A significant difference between Ranch Hands in the high dioxin category and Comparisons was found in the unadjusted analysis of absolute neutrophils (segs). The result was nonsignificant in the adjusted analysis. In both the unadjusted and adjusted analyses of absolute neutrophils (bands) in the continuous form, a marginally significant difference of means was found among Ranch Hands in the low dioxin category and Comparisons. Also, a significant absolute neutrophil (bands) mean difference was found among Ranch Hands in the low and high dioxin categories combined and Comparisons for both the unadjusted and adjusted analyses. Results were consistent in the unadjusted and adjusted analyses of absolute basophils (zero versus nonzero measurements). A significant difference in the proportion of zero absolute basophil measurements was found among Ranch Hands in the low dioxin category and Comparisons. A marginally significant difference was found when contrasting the low and high Ranch Hand dioxin categories with Comparisons. Both results indicate that more Ranch Hands than Comparisons had a zero absolute basophil measurement.

15.4.4 Model 4: 1987 Dioxin

In the unadjusted analyses, several significant and marginally significant results were found. The results are summarized in Table 15-30. Except for the analysis of the discrete form of WBC, each result became nonsignificant in the adjusted analysis. The significant association between continuous WBC count and 1987 dioxin was positive, as were the associations with continuous platelet count and absolute neutrophils (segs). Significant negative associations between 1987 dioxin and the percentage of abnormally low counts were revealed in the discrete analyses of WBC count, hemoglobin, and platelet count. In addition, a marginally significant negative association was found for the percentage of abnormally high hemoglobin counts and 1987 dioxin. For the blood count measures, a marginally significant positive association was found between absolute monocytes and 1987 dioxin.

Table 15-30. Summary of 1987 Dioxin Analysis (Model 4) for Hematology Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Laboratory		
Red Blood Cell (RBC) Count (C)	NS	ns
Red Blood Cell (RBC) Count (D)		
Abnormal Low vs. Normal	ns	ns
Abnormal High vs. Normal	NS	NS
White Blood Cell (WBC) Count (C)	+0.013	NS
White Blood Cell (WBC) Count (D)		
Abnormal Low vs. Normal	−0.020	−0.032
Abnormal High vs. Normal	ns	ns
Hemoglobin (C)	NS	NS
Hemoglobin (D)		
Abnormal Low vs. Normal	−0.049	ns
Abnormal High vs. Normal	ns*	ns
Hematocrit (C)	NS	NS
Hematocrit (D)		
Abnormal Low vs. Normal	ns	ns
Abnormal High vs. Normal	NS	NS
Platelet Count (C)	+0.005	NS
Platelet Count (D)		
Abnormal Low vs. Normal	−0.028	ns
Abnormal High vs. Normal	ns	ns
Prothrombin Time (C)	ns	ns
Prothrombin Time (D)	ns	ns
RBC Morphology	NS	NS
Absolute Neutrophils (Segs) (C)	+0.017	NS
Absolute Neutrophils (Bands) (Nonzero Measurements) (C)	NS	NS
Absolute Neutrophils (Bands) (Zero vs. Nonzero) (D)	ns	ns
Absolute Lymphocytes (C)	NS	NS
Absolute Monocytes (C)	NS*	NS
Absolute Eosinophils (Nonzero Measurements) (C)	ns	ns
Absolute Eosinophils (Zero vs. Nonzero) (D)	NS	ns

Table 15-30. Summary of 1987 Dioxin Analysis (Model 4) for Hematology Variables (Ranch Hands Only) (Continued)

Variable	Unadjusted	Adjusted
Absolute Basophils (Nonzero Measurements) (C)	NS	ns
Absolute Basophils (Zero vs. Nonzero) (D)	ns	ns

Note: NS or ns: Not significant ($p>0.10$).
NS* or ns*: Marginally significant ($0.05<p\leq0.10$).
C: Continuous analysis.
D: Discrete analysis.
+: Slope nonnegative for continuous analysis.
−: Relative risk <1.00 for discrete analysis.

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

15.5 CONCLUSION

Five cell count measures, six measures of absolute blood counts, a coagulation measure, and RBC morphology were analyzed for the hematology assessment. In the analyses of these variables, only platelet count exhibited significant dose-response associations with the indices of dioxin exposure. Ranch Hands enlisted flyers and groundcrew exhibited slightly but significantly higher mean platelet counts than did Comparisons. Ranch Hands in the high dioxin category also exhibited a significantly higher mean platelet count than Comparisons in the continuous analysis. The results in the 1997 follow-up study parallel the findings of the 1987 and 1992 follow-up studies. In conclusion, apart from platelet count, there appears to be little evidence to support a relation between prior dioxin exposure and hematopoietic toxicity.

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16 ENDOCRINE ASSESSMENT

16.1 INTRODUCTION

16.1.1 Background

The essential role of membrane and intracellular receptors in human endocrine function has been firmly established and extensively studied (1). In animal models, much of the basic research into the mechanism of dioxin endocrine toxicity has focused on the dioxin-binding aryl hydrocarbon (Ah) receptor, which has similarities to the endocrine receptors that mediate function of the thyroid, adrenal, and gonadal hormones (2-5).

Animal research has documented that the thyroid is a target organ for dioxin toxicity, although the mechanism has not been defined clearly (6-11). In other studies, dioxin-induced changes in thyroid indices (serum thyroxine [T_4], triiodothyronine [T_3], and thyroid stimulating hormone [TSH]) were directionally different with species and strain specificity (12, 13). The mechanism by which dioxin interacts with or regulates thyroid function in experimental animals remains under investigation. In competing for thyroid hormone binding sites in target organs (14) or by accelerating the metabolism of thyroid hormones by hepatic enzyme induction (15), dioxin administration can induce a mildly hypothyroid state associated with elevated levels of TSH.

How these experimental studies relate to the effect of dioxin on human thyroid function has not been established. The most recently published morbidity reports on the workers exposed to dioxin during a chemical factory explosion in Germany in 1953 included thyroid disorders in the analyses. Across all exposure categories, an increased incidence of thyroid disease was found in workers relative to referents (16). Thyroid disease occurred in 11 of 158 in the exposed cohort but in only two of 161 referents. The heterogeneous mix of thyroid disorders—four cases of thyrotoxicosis, four cases of goiter, two cases of hypothyroidism, and one other unspecified disorder—weighs against a possible relation with dioxin exposure. In the analyses of laboratory measurements from the same exposed population, the authors found positive associations between each of the exposure indices and selected tests of thyroid function, T_4, and thyroxine binding globulin (17). Unfortunately, the most widely used measure of thyroid function—serum TSH—was not included in the analyses.

The finding in laboratory animals of physicochemical similarities between the dioxin-binding Ah and glucocorticoid receptors (5, 18) has prompted further investigation into the interaction of dioxin with other steroid hormones. A review by Couture, et al. (19) provided a comprehensive summary of the research into the developmental toxicity and teratogenicity of dioxin in experimental animals.

Experimental studies have documented numerous adverse male reproductive effects in laboratory animals exposed to dioxin, including reduced testicular weight, impaired spermatogenesis, decreased testicular testosterone secretion, and atrophy of the androgen-sensitive seminal vesicles and epididymis (20-24). Although dioxin administration is associated with diminished testosterone secretion in rats (23, 25, 26), the mechanism is unknown and may involve the hypothalamic-pituitary axis. In rats, dioxin inhibits the secretion of luteinizing hormone (LH) by the pituitary gland, an effect associated with androgen deficiency (27, 28). In other experiments, dioxin inhibited the response of the pituitary to gonadotropin-releasing hormone secreted by the hypothalamus (29).

Additional experiments have explored the effects of dioxin on the pituitary and hypothalamus (30, 31). The use of microsurgical techniques in female rats revealed that dioxin toxicity is aggravated by hypophysectomy, with a sparing effect noted upon administering either corticosterone or thyroid hormone (30). Another study defined a biochemical basis for the effect of dioxin on prolactin levels controlled by the adenohypophysis in female rats (32). Studies on the effects of dioxin on the pituitary-adrenal axis have documented significant suppression of corticosterone production by the adrenal gland (33) and defined a biochemical basis for the apparent reduction in bioactivity of adrenocorticotropic hormone secreted by the pituitary (34).

The National Institute for Occupational Safety and Health (NIOSH) has conducted several long-term epidemiological studies of factory workers who experienced significant occupational exposure to dioxin in chemical production plants (35, 36). In their most recently published report (37), serum levels of three endocrine indices—testosterone, LH, and follicle stimulating hormone (FSH)—were examined in relation to current and calculated initial serum dioxin levels in 248 participants. Current serum dioxin levels were positively and significantly related to both LH and FSH and inversely related to testosterone. In contrast to the NIOSH results, a recent report of the Air Force Health Study (AFHS) population found no relation between the body burden of dioxin and reproductive or endocrine indices, including serum testosterone, FSH, LH, sperm counts and morphology, and anatomic abnormalities of the testes (38).

The possibility that dioxin might affect glucose metabolism in humans was first raised in 1981 with the publication of an occupational study that reported an unusually high prevalence of abnormal glucose tolerance tests (40%) and a 20-percent incidence of diabetes in chemical production workers exposed to dioxin (39). The results of analyses pertinent to glucose metabolism based on serum dioxin data collected during the 1987 and 1992 AFHS examinations recently have been published (40). In the 1987 examination, Ranch Hand participants with the highest serum dioxin levels were nearly three times as likely to have elevations in fasting blood sugar than were Comparisons (41). In the 1992 examination, Ranch Hand participants with high levels of serum dioxin had significantly higher fasting and 2-hour postprandial glucose results than those with lower levels of serum dioxin (42), an effect that was shown to be independent of the serum triglyceride level (43). In nondiabetic Ranch Hands, serum insulin, like the 2-hour postprandial glucose, was positively and significantly associated with current serum dioxin levels. In contrast, in diabetic participants, a consistent inverse dose-response effect was found in all models relating serum insulin to current serum dioxin. Although cause and effect have not been established, these results provide further evidence for an association between glucose intolerance and dioxin levels and raise the possibility that, in a subset of those predisposed to diabetes, dioxin may impair insulin production.

Whether dioxin exposure is in fact a risk factor for the development of diabetes remains controversial. Recent reports from NIOSH noted statistically significantly associations between the prevalence of diabetes and elevated fasting blood sugar with increasing serum dioxin levels (44), although the authors could not exclude confounding by the traditional diabetic risk factors of age, obesity, and family history of diabetes. Other epidemiological studies, some of which have included serum dioxin levels in the analyses, have failed to find an association between glucose intolerance and exposure to dioxin (16, 17, 45).

In the most recent publication by the Institute of Medicine, a special section is devoted to the subject of dioxin exposure as a risk factor for the development of diabetes (46). Based on its comprehensive review of the literature, the committee concluded that "at this time, there is inadequate/insufficient evidence to determine whether an association exists between herbicide or dioxin exposure and increased risk of diabetes."

16.1.2 Summary of Previous Analyses of the Air Force Health Study

16.1.2.1 1982 Baseline Study Summary Results

A laboratory evaluation of the endocrine system was used for analysis in the baseline examination in 1982. Five measures of endocrine status were assessed: T_3 percent uptake, T_4, free thyroxine index (FTI), testosterone, and 2-hour postprandial glucose.

Results showed significant group differences for T_3 percent uptake (abnormally low), predominantly in Ranch Hands 40 years old or younger. The highest percentage of abnormalities was in participants with high body fat. No group difference was noted for elevated 2-hour postprandial glucose values and, as expected, the prevalence of abnormal values was associated with increased age and higher body fat. Lower testosterone values also were associated with increased age and higher body fat. Higher mean testosterone values were significantly more prevalent in the Ranch Hand group. Significant mean shifts were not noted for the T_3 percent uptake, T_4, and the FTI.

These data, coupled with the animal literature on the profound influence of the endocrine system on lethality and body fat metabolism following dioxin exposure, clearly underscored the importance of a more comprehensive evaluation of the endocrine system.

16.1.2.2 1985 Follow-up Study Summary Results

Questionnaire and review-of-systems data for past thyroid disease were similar in both the Ranch Hand and Comparison groups. These historical data were confirmed by a medical records review. Physical examination findings were necessarily limited to data from palpation of the thyroid gland and testicles; the unadjusted results showed no significant group differences.

Evaluation of the endocrine system was conducted primarily by laboratory testing. The thyroid test battery consisted of T_3 percent uptake and TSH, as determined by radioimmunoassay techniques. Testosterone, initial cortisol, differential cortisol (the difference between the initial and 2-hour cortisol levels), and 2-hour postprandial glucose levels also were analyzed. The T_3 percent uptake data showed no group differences for either mean values or frequency of abnormally low or high values. TSH results revealed a significantly higher mean level in the Ranch Hand group, but this difference was not detected by discrete analysis of the proportions of abnormally high TSH results.

The mean level of testosterone remained significantly elevated for Ranch Hands, as contrasted with Comparisons, in the 10 to 25 percent body fat category, but this difference was not reflected in the discrete analyses. For the few participants with less than 10 percent body fat (six Ranch Hands, four Comparisons), mean testosterone levels were lower for Ranch Hands than for Comparisons.

Two timed cortisol specimens showed no significant group differences in mean values or the percentage of participants with abnormalities. The difference between the timed cortisol results, termed the "differential cortisol," showed no significant group differences for non-Blacks or Blacks born before 1942, but Black Ranch Hands born in or after 1942 had a lower mean differential cortisol level than did their Comparisons.

Group means of 2-hour postprandial glucose levels were not statistically different, but discrete analyses revealed that there was a significantly higher frequency of glucose-impaired (at least 140 mg/dl, but less than 200 mg/dl) Comparisons than Ranch Hands. A variable comprising known diabetics and individuals classified as diabetic by the glucose tolerance test showed no difference between the Ranch Hand and

Comparison groups. The covariates age, race, and body fat were significantly associated with diabetes in this analysis.

16.1.2.3 1987 Follow-up Study Summary Results

The endocrine assessment did not disclose any statistically significant differences between the Ranch Hand and Comparison groups. The percentage of participants who indicated problems with current thyroid disease was similar between groups, as were the percentages with thyroid and testicular abnormalities determined by palpation at the physical examination. The Ranch Hand TSH mean was marginally significantly higher than the Comparison TSH mean. Ranch Hand and Comparison mean levels were similar for T_3 percent uptake, FSH, testosterone, and 2-hour postprandial glucose. The percentage of Ranch Hands with abnormal values for these five laboratory variables was higher than the percentage of Comparisons with abnormal values; however, the difference in the percentage of abnormal values between Ranch Hands and Comparisons was not statistically significant for these five laboratory variables. In addition, analyses were performed on a composite diabetes indicator. A participant was considered diabetic for this indicator if he had a verified history of diabetes or had a 2-hour postprandial glucose level of at least 200 mg/dl. The difference in the percentage of Ranch Hands and Comparisons considered diabetic, as determined through this composite diabetes indicator, was not significant.

16.1.2.4 Serum Dioxin Analysis of 1987 Follow-up Study Summary Results

The endocrine assessment found a strong positive association between initial dioxin and diabetes prevalence and testes abnormalities; however, the analyses of current dioxin levels in Ranch Hands and Comparisons indicated that the increased risk was apparent only for Ranch Hands in the high current dioxin category (>33.3 parts per trillion [ppt]). These Ranch Hands also had significantly higher mean levels of TSH, fasting glucose, and 2-hour postprandial glucose than background Comparisons, as well as lower mean levels of T_3 percent uptake and testosterone. The discrete analyses of these variables found a significant increase in abnormally elevated fasting glucose levels and diabetic 2-hour postprandial glucose levels as both initial dioxin and current dioxin increased.

16.1.2.5 1992 Follow-up Study Summary Results

The assessment of the endocrine system included an extensive evaluation of thyroid, pancreatic, and gonadal functions and their relation to dioxin exposure. Analyses of thyroid functions did not identify significant differences between Ranch Hands and Comparisons. Similarly, the prevalence of diabetes in the two populations was not significantly different, although significant positive associations were found between time to the onset of diabetes and both lipid-adjusted and whole weight dioxin levels, as measured in 1987.

Significant glucose metabolism results were confined to the current serum dioxin analyses. These results suggested a possible mechanism for dioxin effect on glucose metabolism and the development of diabetes. Diabetic Ranch Hands with high levels of current serum dioxin had significantly higher fasting glucose levels than those with lower levels of dioxin. Nondiabetic Ranch Hands, on the other hand, exhibited an inverse association between fasting glucose and current serum dioxin and a positive association between 2-hour postprandial glucose and current serum dioxin. Serum dioxin levels were significantly related to elevated insulin levels in nondiabetic, but not in diabetic Ranch Hands. This was suggestive of a dioxin effect on glucose metabolism with a heightened release of insulin in Ranch Hands with a fully responsive pancreas. When this pancreatic response is no longer effective, elevated glucose levels lead to the clinical diagnosis of diabetes and loss of the dose-response between dioxin and insulin.

Analyses of gonadal functions detected a significant inverse dose-response relation between current serum dioxin and total serum testosterone in Ranch Hands. These results supported those described in the Serum Dioxin Analysis of the 1987 Follow-up Examination, but the clinical meaning was uncertain.

In conclusion, although the existence of endocrine disorders was comparable in Ranch Hands and Comparisons, the assessment of glucose metabolism showed the possibility of adverse effects from dioxin in relation to glucose intolerance and insulin production.

16.1.3 Parameters for the 1997 Endocrine Assessment

16.1.3.1 Dependent Variables

Questionnaire, physical examination, and laboratory data collected at the AFHS 1997 follow-up examination were used in the endocrine assessment. The self-reported information collected from the 1997 questionnaire was subsequently verified and analyses were based on the verified data.

16.1.3.2 Medical Records Data

The 1997 questionnaire posed a general screening question on thyroid function and disease. Each participant was asked the following question during the in-person health interview: "Since the date of the last interview, has a doctor told you for the first time that you had thyroid problems?" All affirmative responses were verified by a medical records review and added to previously reported and verified information on the thyroid function from the 1982 baseline examination and the 1985, 1987, and 1992 follow-up examinations for each participant. Thyroid disease was classified according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic codes. The ICD-9-CM codes for thyroid disease encompassed 240.0-246.9. Based on the verified data, history of thyroid disease was classified as "yes" or "no." Participants with a pre-Southeast Asia (SEA) history of thyroid disease were excluded from the analysis of thyroid disease history.

Similar information was asked of each participant regarding diabetes. This information also was verified and combined with previous information. ICD-9-CM codes 250.00-250.93 were used to classify diabetes. Participants with a verified history of diabetes were combined with those participants with a 2-hour postprandial glucose level of 200 mg/dl or greater at the 1997 physical examination and classified as "yes" for a composite diabetes indicator variable. Those participants without a verified history of diabetes and with a 2-hour postprandial glucose level of less than 200 mg/dl at the 1997 physical examination were classified as "no." This composite diabetes indicator, derived from a medical records review and laboratory results, was analyzed as part of the endocrine assessment. Participants classified as "yes" were designated as diabetics and participants classified as "no" were designated as nondiabetics.

After the data were analyzed, medical records of all participants designated as diabetic, based on medical records, were reviewed to determine diabetic type (1 or 2). One participant (a Ranch Hand veteran) was diagnosed as having type 1 (insulin-dependent) diabetes and the remainder were diagnosed as having type 2 (adult onset) diabetes. A reanalysis with the single Ranch Hand with type 1 diabetes excluded yielded the same results as those already presented.

As part of the 1997 questionnaire, questions were asked of diabetics regarding the use of insulin, oral diabetes medication, and diet. This self-reported information was verified and a diabetic severity index was constructed and analyzed for all participants. This index was categorized as "requiring insulin," "oral hypoglycemic," "diet only," or "no treatment" for diabetics and "no diabetes" for nondiabetics.