

Table 14-34. Longitudinal Analysis of Popliteal Pulses (Continued)

Dioxin Category	Normal in 1985		Adj. Relative Risk (95% C.I.) ^a	p-Value ^b
	n in 1997	Number (%) Abnormal in 1997		
Comparison	1,017	23 (2.3)		
Background RH	353	8 (2.3)	0.87 (0.38,1.97)	0.731
Low RH	224	7 (3.1)	1.30 (0.55,3.09)	0.555
High RH	238	7 (2.9)	1.79 (0.75,4.30)	0.193
Low plus High RH	462	14 (3.0)	1.53 (0.77,3.03)	0.221

^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.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin \leq 10 ppt.

Background (Ranch Hand): 1987 Dioxin \leq 10 ppt.

Low (Ranch Hand): 1987 Dioxin >10 ppt, 10 ppt $<$ Initial Dioxin \leq 94 ppt.

High (Ranch Hand): 1987 Dioxin >10 ppt, Initial Dioxin $>$ 94 ppt.

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

14.2.3.1.5 Dorsalis Pedis Pulses

The longitudinal analyses in Models 1 through 3 did not reveal any significant associations between dioxin and the change in dorsalis pedis pulses (Table 14-35(a-c): p>0.33 for each analysis).

Table 14-35. Longitudinal Analysis of Dorsalis Pedis Pulses

		Number (%) Abnormal/(n)		
Occupational Category	Group	Examination		
		1985	1992	1997
<i>All</i>	<i>Ranch Hand</i>	94 (11.4) (821)	60 (7.5) (798)	67 (8.2) (821)
	<i>Comparison</i>	111 (10.6) (1,044)	70 (6.9) (1,017)	85 (8.1) (1,044)
Officer	Ranch Hand	41 (12.9) (318)	23 (7.4) (312)	27 (8.5) (318)
	Comparison	43 (10.5) (409)	28 (7.0) (402)	30 (7.3) (409)
Enlisted Flyer	Ranch Hand	16 (11.0) (145)	9 (6.3) (143)	18 (12.4) (145)
	Comparison	23 (14.6) (158)	16 (10.3) (156)	13 (8.2) (158)
Enlisted Groundcrew	Ranch Hand	37 (10.3) (358)	28 (8.2) (343)	22 (6.1) (358)
	Comparison	45 (9.4) (477)	26 (5.7) (459)	42 (8.8) (477)

Table 14-35. Longitudinal Analysis of Dorsalis Pedis Pulses (Continued)

Occupational Category	Group	Normal in 1985		Adj. Relative Risk (95% C.I.) ^a	p-Value ^a
		n in 1997	Number (%) Abnormal in 1997		
All	Ranch Hand	727	50 (6.9)	0.97 (0.66,1.43)	0.894
	Comparison	933	66 (7.1)		
Officer	Ranch Hand	277	22 (7.9)	1.07 (0.59,1.93)	0.821
	Comparison	366	27 (7.4)		
Enlisted Flyer	Ranch Hand	129	12 (9.3)	1.42 (0.58,3.52)	0.444
	Comparison	135	9 (6.7)		
Enlisted	Ranch Hand	321	16 (5.0)	0.73 (0.39,1.38)	0.335
Groundcrew	Comparison	432	30 (6.9)		

^a Relative risk, confidence interval, and p-values are in reference to a contrast of 1985 and 1997 results; results adjusted for age in 1997.

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

(b) MODEL 2: RANCH HANDS — INITIAL DIOXIN

Initial Dioxin	Number (%) Abnormal/(n)		
	1985	1992	1997
Low	14 (9.4) (149)	8 (5.6) (144)	12 (8.1) (149)
Medium	20 (12.7) (158)	14 (9.0) (155)	16 (10.1) (158)
High	12 (7.8) (154)	9 (6.0) (149)	10 (6.5) (154)

Initial Dioxin Category Summary Statistics	Analysis Results for Log ₂ (Initial Dioxin) ^a			
	Normal in 1985		Adj. Relative Risk (95% C.I.) ^b	p-Value
Initial Dioxin	n in 1997	Number (%) Abnormal in 1997		
Low	135	10 (7.4)	1.01 (0.72,1.41)	0.946
Medium	138	11 (8.0)		
High	142	7 (4.9)		

^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.

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

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

Table 14-35. Longitudinal Analysis of Dorsalis Pedis Pulses (Continued)

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

Dioxin Category	Number (%) Abnormal/(n)		
	1985	1992	1997
Comparison	108 (10.6) (1,016)	70 (7.1) (991)	85 (8.4) (1,016)
Background RH	48 (13.5) (355)	29 (8.4) (345)	29 (8.2) (355)
Low RH	21 (9.4) (224)	12 (5.5) (217)	22 (9.8) (224)
High RH	25 (10.5) (237)	19 (8.2) (231)	16 (6.8) (237)
Low plus High RH	46 (10.0) (461)	31 (6.9) (448)	38 (8.2) (461)

Normal in 1985				
Dioxin Category	n in 1997	Number (%) Abnormal in 1997	Adj. Relative Risk (95% C.I.) ^a	p-Value ^b
Comparison	908	66 (7.3)		
Background RH	307	22 (7.2)	0.89 (0.53,1.48)	0.650
Low RH	203	17 (8.4)	1.08 (0.61,1.89)	0.798
High RH	212	11 (5.2)	0.91 (0.47,1.78)	0.789
Low plus High RH	415	28 (6.7)	0.99 (0.62,1.59)	0.964

^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.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin \leq 10 ppt.

Background (Ranch Hand): 1987 Dioxin \leq 10 ppt.

Low (Ranch Hand): 1987 Dioxin >10 ppt, 10 ppt $<$ Initial Dioxin \leq 94 ppt.

High (Ranch Hand): 1987 Dioxin >10 ppt, Initial Dioxin $>$ 94 ppt.

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

14.2.3.1.6 Posterior Tibial Pulses

Model 1 and 2 analyses did not show any significant associations between dioxin and the change in posterior tibial pulses between 1985 and 1997 (Table 14-36(a,b): $p>0.12$ for each analysis).

Model 3 analysis of the change in posterior tibial pulses from normal in 1985 to abnormal in 1997 revealed one significant and one marginally significant contrast: Ranch Hands in the high dioxin category versus Comparisons (Table 14-36(c): Adj. RR=1.70, $p=0.090$) and Ranch Hands in the low plus high dioxin category versus Comparisons (Table 14-36(c): Adj. RR=1.60, $p=0.047$). Of the Comparisons, 5.1 percent had normal posterior tibial pulses in 1985 and abnormal posterior tibial pulses

in 1997. Of the Ranch Hands, 6.3 percent in the high dioxin category and 7.2 percent in the low plus high dioxin category had normal posterior tibial pulses in 1985 and abnormal posterior tibial pulses in 1997.

Table 14-36. Longitudinal Analysis of Posterior Tibial Pulses

(a) MODEL 1: RANCH HANDS VS. COMPARISONS

Occupational Category	Group	Number (%) Abnormal/(n) Examination		
		1985	1992	1997
<i>All</i>	<i>Ranch Hand</i>	2 (0.2) (822)	20 (2.5) (801)	56 (6.8) (822)
	<i>Comparison</i>	6 (0.6) (1,044)	22 (2.2) (1,017)	58 (5.6) (1,044)
Officer	Ranch Hand	1 (0.3) (318)	9 (2.9) (313)	21 (6.6) (318)
	Comparison	2 (0.5) (411)	10 (2.5) (404)	23 (5.6) (411)
Enlisted Flyer	Ranch Hand	1 (0.7) (145)	5 (3.5) (143)	14 (9.7) (145)
	Comparison	1 (0.6) (156)	4 (2.6) (154)	10 (6.4) (156)
Enlisted Groundcrew	Ranch Hand	0 (0.0) (359)	6 (1.7) (345)	21 (5.8) (359)
	Comparison	3 (0.6) (477)	8 (1.7) (459)	25 (5.2) (477)

Occupational Category	Group	Normal in 1985		
		n in 1997	Number (%) Abnormal in 1997	Adj. Relative Risk (95% C.I.) ^a
<i>All</i>	<i>Ranch Hand</i>	820	56 (6.8)	1.36 (0.92,2.01)
	<i>Comparison</i>	1,038	53 (5.1)	
Officer	Ranch Hand	317	21 (6.6)	1.29 (0.69,2.43)
	Comparison	409	21 (5.1)	
Enlisted Flyer	Ranch Hand	144	14 (9.7)	1.70 (0.70,4.09)
	Comparison	155	9 (5.8)	
Enlisted Groundcrew	Ranch Hand	359	21 (5.8)	1.26 (0.68,2.35)
	Comparison	474	23 (4.9)	

^a Relative risk, confidence interval, and p-values are in reference to a contrast of 1985 and 1997 results; results adjusted for age in 1997.

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

Table 14-36. Longitudinal Analysis of Posterior Tibial Pulses (Continued)

(b) MODEL 2: RANCH HANDS — INITIAL DIOXIN

Initial Dioxin	Number (%) Abnormal(n)		
	1985	1992	1997
Low	1 (0.7) (149)	5 (3.5) (144)	9 (6.0) (149)
Medium	0 (0.0) (158)	5 (3.2) (155)	15 (9.5) (158)
High	1 (0.6) (155)	2 (1.3) (151)	9 (5.8) (155)

Initial Dioxin Category Summary Statistics		Analysis Results for \log_2 (Initial Dioxin) ^a		
Normal in 1985				
Initial Dioxin	n in 1997	Number (%) Abnormal in 1997	Adj. Relative Risk (95% C.L.) ^b	p-Value
Low	148	9 (6.1)	1.12 (0.85, 1.49)	0.418
Medium	158	15 (9.5)		
High	154	9 (5.8)		

^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.

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

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

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

Dioxin Category	Number (%) Abnormal(n)		
	1985	1992	1997
Comparison	6 (0.6) (1,016)	22 (2.2) (991)	57 (5.6) (1,016)
Background RH	0 (0.0) (355)	7 (2.0) (346)	22 (6.2) (355)
Low RH	1 (0.4) (224)	6 (2.8) (217)	18 (8.0) (224)
High RH	1 (0.4) (238)	6 (2.6) (233)	15 (6.3) (238)
Low plus High RH	2 (0.4) (462)	12 (2.7) (450)	33 (7.1) (462)

Table 14-36. Longitudinal Analysis of Posterior Tibial Pulses (Continued)

Dioxin Category	Normal in 1985		Adj. Relative Risk (95% C.I.) ^{ab}	p-Value ^b
	n in 1997	Number (%) Abnormal in 1997		
Comparison	1,010	52 (5.1)		
Background RH	355	22 (6.2)	1.05 (0.62,1.77)	0.856
Low RH	223	18 (8.1)	1.50 (0.85,2.65)	0.160
High RH	237	15 (6.3)	1.70 (0.92,3.12)	0.090
Low plus High RH	460	33 (7.2)	1.60 (1.01,2.54)	0.047

^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.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin \leq 10 ppt.

Background (Ranch Hand): 1987 Dioxin \leq 10 ppt.

Low (Ranch Hand): 1987 Dioxin >10 ppt, 10 ppt $<$ Initial Dioxin \leq 94 ppt.

High (Ranch Hand): 1987 Dioxin >10 ppt, Initial Dioxin $>$ 94 ppt.

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

14.2.3.1.7 Leg Pulses

The longitudinal analyses in Models 1 through 3 did not reveal a significant association between dioxin and the change from normal leg pulses in 1985 to abnormal leg pulses in 1997 (Table 14-37(a-c): $p>0.15$ for each analysis).

Table 14-37. Longitudinal Analysis of Leg Pulses

(a) MODEL 1: RANCH HANDS VS. COMPARISONS

Occupational Category	Group	Number (%) Abnormal/(n) Examination		
		1985	1992	1997
<i>All</i>	<i>Ranch Hand</i>	97 (11.8) (821)	66 (8.3) (798)	91 (11.1) (821)
	<i>Comparison</i>	114 (10.9) (1,042)	77 (7.6) (1,015)	109 (10.5) (1,042)
Officer	Ranch Hand	43 (13.5) (318)	24 (7.7) (312)	35 (11.0) (318)
	Comparison	44 (10.8) (409)	29 (7.2) (402)	38 (9.3) (409)
Enlisted Flyer	Ranch Hand	17 (11.7) (145)	11 (7.7) (143)	25 (17.2) (145)
	Comparison	22 (14.1) (156)	16 (10.4) (154)	17 (10.9) (156)
Enlisted Groundcrew	Ranch Hand	37 (10.3) (358)	31 (9.0) (343)	31 (8.7) (358)
	Comparison	48 (10.1) (477)	32 (7.0) (459)	54 (11.3) (477)

Table 14-37. Longitudinal Analysis of Leg Pulses (Continued)

Occupational Category	Group	Normal in 1985		Adj. Relative Risk (95% C.I.) ^a	p-Value ^a
		n in 1997	Number (%) Abnormal in 1997		
All	Ranch Hand	724	73 (10.1)	1.12 (0.80,1.57)	0.502
	Comparison	928	85 (9.2)		
Officer	Ranch Hand	275	29 (10.5)	1.13 (0.67,1.93)	0.645
	Comparison	365	34 (9.3)		
Enlisted Flyer	Ranch Hand	128	19 (14.8)	1.76 (0.81,3.83)	0.153
	Comparison	134	12 (9.0)		
Enlisted	Ranch Hand	321	25 (7.8)	0.89 (0.52,1.52)	0.676
Groundcrew	Comparison	429	39 (9.1)		

^a Relative risk, confidence interval, and p-values are in reference to a contrast of 1985 and 1997 results; results adjusted for age in 1997.

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

(b) MODEL 2: RANCH HANDS — INITIAL DIOXIN

Initial Dioxin	Number (%) Abnormal/n Examination		
	1985	1992	1997
Low	15 (10.1) (149)	9 (6.3) (144)	15 (10.1) (149)
Medium	20 (12.7) (158)	17 (11.0) (155)	22 (13.9) (158)
High	13 (8.4) (154)	9 (6.0) (149)	14 (9.1) (154)

Initial Dioxin Category Summary Statistics		Analysis Results for Log ₂ (Initial Dioxin) ^a		
Normal in 1985				
Initial Dioxin	n in 1997	Number (%) Abnormal in 1997	Adj. Relative Risk (95% C.I.) ^b	p-Value
Low	134	13 (9.7)	1.14 (0.87,1.49)	0.344
Medium	138	17 (12.3)		
High	141	11 (7.8)		

^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.

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

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

Table 14-37. Longitudinal Analysis of Leg Pulses (Continued)

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

Dioxin Category	Number (%) Abnormal/(n) Examination		
	1985	1992	1997
Comparison	111 (10.9) (1,014)	77 (7.8) (989)	108 (10.7) (1,014)
Background RH	49 (13.8) (355)	30 (8.7) (345)	39 (11.0) (355)
Low RH	22 (9.8) (224)	13 (6.0) (217)	29 (12.9) (224)
High RH	26 (11.0) (237)	22 (9.5) (231)	22 (9.3) (237)
Low plus High RH	48 (10.4) (461)	35 (7.8) (448)	51 (11.1) (461)

Dioxin Category	Normal in 1985		Adj. Relative Risk (95% C.I.) ^a	p-Value ^b
	n in 1997	Number (%) Abnormal in 1997		
Comparison	903	84 (9.3)		
Background RH	306	31 (10.1)	0.98 (0.63,1.52)	0.924
Low RH	202	24 (11.9)	1.21 (0.74,1.97)	0.455
High RH	211	17 (8.1)	1.17 (0.67,2.04)	0.589
Low plus High RH	413	41 (9.9)	1.19 (0.79,1.78)	0.411

^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.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin \leq 10 ppt.

Background (Ranch Hand): 1987 Dioxin \leq 10 ppt.

Low (Ranch Hand): 1987 Dioxin $>$ 10 ppt, 10 ppt $<$ Initial Dioxin \leq 94 ppt.

High (Ranch Hand): 1987 Dioxin $>$ 10 ppt, Initial Dioxin $>$ 94 ppt.

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

14.2.3.1.8 Peripheral Pulses

The change from normal peripheral pulses in 1985 to abnormal peripheral pulses in 1997 was not significantly associated with dioxin in Models 1 through 3 (Table 14-38(a-c): $p > 0.15$ for each analysis).

Table 14-38. Longitudinal Analysis of Peripheral Pulses

(a) MODEL 1: RANCH HANDS VS. COMPARISONS

Occupational Category	Group	Number (%) Abnormal/(n) Examination		
		1985	1992	1997
<i>All</i>	<i>Ranch Hand</i>	97 (11.8) (821)	66 (8.3) (798)	94 (11.4) (821)
	<i>Comparison</i>	116 (11.1) (1,041)	81 (8.0) (1,014)	112 (10.8) (1,041)
Officer	Ranch Hand	43 (13.5) (318)	24 (7.7) (312)	36 (11.3) (318)
	Comparison	44 (10.8) (409)	30 (7.5) (402)	40 (9.8) (409)
Enlisted Flyer	Ranch Hand	17 (11.7) (145)	11 (7.7) (143)	25 (17.2) (145)
	Comparison	22 (14.1) (156)	16 (10.4) (154)	17 (10.9) (156)
Enlisted Groundcrew	Ranch Hand	37 (10.3) (358)	31 (9.0) (343)	33 (9.2) (358)
	Comparison	50 (10.5) (476)	35 (7.6) (458)	55 (11.6) (476)

Occupational Category	Group	Normal in 1985			Adj. Relative Risk (95% C.I.) ^a	p-Value ^a
		n in 1997	Number (%) Abnormal in 1997			
<i>All</i>	<i>Ranch Hand</i>	724	76 (10.5)		1.14 (0.82,1.59)	0.433
	<i>Comparison</i>	925	87 (9.4)			
Officer	Ranch Hand	275	30 (10.9)		1.10 (0.66,1.86)	0.710
	Comparison	365	36 (9.9)			
Enlisted Flyer	Ranch Hand	128	19 (14.8)		1.76 (0.81,3.83)	0.154
	Comparison	134	12 (9.0)			
Enlisted Groundcrew	Ranch Hand	321	27 (8.4)		0.97 (0.57,1.64)	0.901
	Comparison	426	39 (9.2)			

^a Relative risk, confidence interval, and p-values are in reference to a contrast of 1985 and 1997 results; results adjusted for age in 1997.

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

Table 14-38. Longitudinal Analysis of Peripheral Pulses (Continued)

(b) MODEL 2: RANCH HANDS — INITIAL DIOXIN

Initial Dioxin	Number (%) Abnormal/(n)		
	1985	1992	1997
Low	15 (10.1) (149)	9 (6.3) (144)	16 (10.7) (149)
Medium	20 (12.7) (158)	17 (11.0) (155)	22 (13.9) (158)
High	13 (8.4) (154)	9 (6.0) (149)	15 (9.7) (154)

Initial Dioxin Category Summary Statistics		Analysis Results for \log_2 (Initial Dioxin) ^a		
Normal in 1985		Adj. Relative Risk (95% C.I.) ^b	p-Value	
Initial Dioxin	n in 1997	Number (%) Abnormal in 1997		
Low	134	14 (10.4)	1.11 (0.85,1.45)	0.434
Medium	138	17 (12.3)		
High	141	12 (8.5)		

^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.

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

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

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

Dioxin Category	Number (%) Abnormal/(n)		
	1985	1992	1997
Comparison	113 (11.2) (1,013)	81 (8.2) (988)	111 (11.0) (1,013)
Background RH	49 (13.8) (355)	30 (8.7) (345)	40 (11.3) (355)
Low RH	22 (9.8) (224)	13 (6.0) (217)	30 (13.4) (224)
High RH	26 (11.0) (237)	22 (9.5) (231)	23 (9.7) (237)
Low plus High RH	48 (10.4) (461)	35 (7.8) (448)	53 (11.5) (461)

Table 14-38. Longitudinal Analysis of Peripheral Pulses (Continued)

Dioxin Category	Normal in 1985		Adj. Relative Risk (95% C.I.) ^a	p-Value ^b
	n in 1997	Number (%) Abnormal in 1997		
Comparison	900	86 (9.6)		
Background RH	306	32 (10.5)	0.98 (0.63,1.52)	0.934
Low RH	202	25 (12.4)	1.23 (0.76,1.99)	0.408
High RH	211	18 (8.5)	1.22 (0.70,2.11)	0.482
Low plus High RH	413	43 (10.4)	1.22 (0.82,1.82)	0.325

^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.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin \leq 10 ppt.

Background (Ranch Hand): 1987 Dioxin \leq 10 ppt.

Low (Ranch Hand): 1987 Dioxin >10 ppt, 10 ppt $<$ Initial Dioxin \leq 94 ppt.

High (Ranch Hand): 1987 Dioxin >10 ppt, Initial Dioxin $>$ 94 ppt.

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

14.3 DISCUSSION

Cardiovascular diseases are among the most common encountered by the primary care physician. In practice, the diagnosis of cardiovascular disease is based primarily on the noninvasive data analyzed in the current chapter. Specifically, the history, physical examination, chest x ray, and resting ECG remain highly reliable indices that can alert the clinician to the presence of underlying cardiovascular disease and indicate the need for additional, more specific, noninvasive or invasive studies. Although arbitrary, dividing data collection into central and peripheral cardiovascular functions is convenient and forms a reasonable basis for comparison of the cohorts under study.

The limitations of the history in cardiovascular diagnosis deserve emphasis. In peripheral vascular disease, for example, signs and symptoms will vary depending on the degree of development of collateral circulatory channels. While hemodynamically significant arterial disease of the lower extremities is usually associated with claudication, severe carotid occlusive disease can be present in the absence of symptoms of transient cerebral ischemia. Further, conclusive evidence shows that advanced coronary artery disease can occur in the absence of angina and be present as "silent" myocardial ischemia. Lastly, it is well recognized that the cardiovascular history, as related by patients, is often subject to error. The generic term "heart attack," for example, can be used to describe any type of cardiac event from an isolated episode of unstable angina or arrhythmia to a myocardial infarction. These imperfections highlight the importance of the medical record verification conducted in this study.

In the cardiovascular assessment particularly, the physical examination can provide valuable clues to the presence of asymptomatic but significant underlying disease. Steps were taken to simplify data collection and reduce differences among the examining physicians. All blood pressure readings, for example, were taken by automated sphygmomanometric instruments. Auscultatory endpoints—murmurs and bruits—were recorded as present or absent by anatomic location, thus eliminating speculation as to specific

valvular or vessel origin and hemodynamic significance. As markers of occult arterial occlusive disease, vascular bruits are relatively easy to detect and were carefully sought over the carotid, abdominal, and femoral vessels.

The data relevant to this chapter included the resting ECG, the standard two-view chest x ray (discussed in Chapter 18, Pulmonary Assessment) and Doppler arterial vascular studies. The test used can confirm diagnoses that can be made based on data available in the current assessment. For example, when correlated with the history and physical examination, the chest x ray and ECG enable the clinician to draw highly accurate conclusions regarding the presence and hemodynamic significance of valvular heart disease of any etiology. As defined by the chest x ray, the pulmonary vascularity can provide reliable clues to the presence of global left ventricular dysfunction with pulmonary venous congestion and of pulmonary hypertension of any cause.

In the analyses of verified historical variables, hypertension, myocardial infarction, transient ischemic attack, and stroke were similar in Ranch Hands and Comparisons. In the 1997 examinations, in contrast to 1992, Ranch Hands were more likely to have a history of heart disease (66.1% vs. 60.8%) across all occupational strata, particularly in the enlisted flyer category. In none of the physical examination or electrocardiographic variables were any significant group differences defined. The prevalence of funduscopic abnormalities, peripheral pulse deficits, and intermittent claudication, all more common in Ranch Hands than Comparisons in the 1992 examination, is now essentially the same in the two cohorts.

Serum dioxin analyses yielded several significant results. In the unadjusted analysis, a significant positive dose-response effect was noted in Ranch Hands in the association of hypertension with 1987 serum dioxin levels (34.0%, 38.0%, and 49.1% in the low, medium, and high categories, respectively), an association that remained significant after adjustment for covariates. Similarly, although the association was less significant, a positive dose-response effect was noted between the electrocardiographic evidence of a myocardial infarction and both initial and 1987 serum dioxin levels. Ranch Hands in the highest dioxin category were more likely than Comparisons to have tachycardia, as determined by the electrocardiograph. In contrast, although Ranch Hands were more likely than Comparisons to have a history of heart disease, a significant inverse dose-response effect was noted in relation to both extrapolated initial and 1987 serum dioxin levels. These results are consistent with those from both the 1987 and 1992 examinations.

With few exceptions, dependent variable-covariate analyses confirmed well-established associations. By a medical records review and by abnormalities detected on physical examinations, cardiovascular disease was associated significantly with the classic risk factors of age, cigarette use, and, particularly, diabetes. Obesity proved to be a significant risk factor for the development of heart disease and for numerous electrocardiographic abnormalities but not to the occurrence of myocardial infarction historically or by ECG. Alcohol consumption was associated strongly with the development of hypertension but did not have the protective effect on the occurrence of myocardial infarction that was noted in the 1992 examination. The increased prevalence of pulse deficits in association with alcohol consumption may have been mediated by concomitant cigarette use. Finally, consistent with the results of the 1987 and 1992 examinations, type A personality traits were not found to be associated with an increased risk for the development of cardiovascular disease.

In the longitudinal analysis, a comparable increase in the prevalence of peripheral pulse deficits was noted in both the Ranch Hand and Comparison cohorts between the 1992 and 1997 examinations. Although none of the group differences was statistically significant, Ranch Hands continued to have a slightly greater prevalence of pulse deficits than Comparisons at all sites examined. Two of the six analyses, the posterior tibial and femoral pulses, yielded evidence for a significant or marginally significant association

of pulse deficits with categorized dioxin. Consistent with all previous examinations, Comparisons were found to be at slightly greater risk than Ranch Hands for the development of systolic hypertension by discrete analysis, but group differences remain nonsignificant.

In contrast to prior examinations, the current study has documented that Ranch Hands are more likely than Comparisons to have historical evidence for heart disease (excluding essential hypertension) but are no longer at greater risk for the occurrence of pulse deficits. By all other indices, the prevalence of cardiovascular disease appears similar in both cohorts. For the first time, there is evidence that dioxin exposure may be a risk factor for the development of hypertension and myocardial infarction. As of 1997, the verified history of essential hypertension was associated with 1987 dioxin, and the evidence of prior myocardial infarction from the ECG was associated with initial dioxin.

14.4 SUMMARY

The cardiovascular assessment was based on a medical records review and verification, physical examination and ECG determinations, and an ICVI index based on participant responses to three questions regarding leg pain. Variables constructed from the medical records review included essential hypertension, heart disease (excluding essential hypertension), myocardial infarction, and stroke or transient ischemic attack. The physical examination findings, the ECG determinations, and the ICVI index investigated the central cardiac function and peripheral vascular function. Each health endpoint was examined for an association with exposure group (Model 1), initial dioxin (Model 2), categorized dioxin (Model 3), and 1987 dioxin levels (Model 4). Significant results from the adjusted analyses are presented below.

14.4.1 Model 1: Group Analysis

The adjusted group analysis revealed that Ranch Hands had a significantly higher percentage of participants with a history of heart disease (excluding essential hypertension) than did Comparisons when all occupational strata were combined. Stratifying by occupation revealed a significantly higher percentage of Ranch Hand enlisted flyers with a history of heart disease than Comparison enlisted flyers. Ranch Hand enlisted groundcrew had a significantly lower percentage of abnormal funduscopic examination results than Comparison enlisted groundcrew. Ranch Hand enlisted groundcrew also had a marginally significantly lower percentage of abnormal overall ECG findings than Comparison enlisted groundcrew. The results of all unadjusted and adjusted Model 1 analyses are summarized in Table 14-39.

Table 14-39. Summary of Group Analysis (Model 1) for Cardiovascular Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Medical Records				
Essential Hypertension (D)	ns	ns	NS	ns
Heart Disease (Excluding Essential Hypertension) (D)	+0.013	NS	+0.003	NS
Myocardial Infarction (D)	NS	ns	NS	NS
Stroke or Transient Ischemic Attack (D)	NS	NS	ns	NS
Physical Examination				
Systolic Blood Pressure (C)	ns	ns	ns	ns
Systolic Blood Pressure (D)	ns	NS	NS	ns

Table 14-39. Summary of Group Analysis (Model 1) for Cardiovascular Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	UNADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Diastolic Blood Pressure (C)	ns	ns	NS	ns
Diastolic Blood Pressure (D)	NS	NS	NS	ns
Heart Sounds (D)	ns	ns	ns	ns
Overall Electrocardiograph (ECG) (D)	NS	NS	NS	ns*
ECG: Right Bundle Branch Block (D)	ns	ns	NS	ns
ECG: Left Bundle Branch Block (D)	ns	ns	NS	ns
ECG: Non-Specific ST- and T-Wave Changes (D)	NS	NS	NS	ns
ECG: Bradycardia (D)	ns	ns	NS	ns
ECG: Tachycardia (D)	NS	NS	NS	NS
ECG: Arrhythmia (D)	NS	NS	NS	ns
ECG: Evidence of Prior Myocardial Infarction (D)	ns	ns	ns	ns
ECG: Other Diagnoses (D)	NS	NS	--	NS
Funduscopic Examination (D)	ns	NS	NS	-0.033
Carotid Bruits (D)	NS	ns	NS	ns
Radial Pulses (D)	NS	NS	--	NS
Femoral Pulses (D)	NS*	NS	NS	NS
Popliteal Pulses (D)	NS	ns	NS	NS
Dorsalis Pedis Pulses (D)	NS	NS	NS	ns
Posterior Tibial Pulses (D)	NS	NS	NS	NS
Leg Pulses (D)	NS	NS	NS	ns
Peripheral Pulses (D)	NS	NS	NS	ns
Self-reported Questionnaire				
Intermittent Claudication and Vascular Insufficiency Index (ICVI) (D)	NS	NS	ns	NS

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

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

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk ≥ 1.00 .

-: Relative risk < 1.00 .

--: Analysis not performed because of the sparse number of participants with an abnormality.

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

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 a relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Table 14-39. Summary of Group Analysis (Model 1) for Cardiovascular Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	All	Officer	ADJUSTED		
			Enlisted Flyer	Enlisted Groundcrew	
Medical Records					
Essential Hypertension (D)	ns	ns	NS	ns	
Heart Disease (Excluding Essential Hypertension) (D)	+0.018	NS	+0.004	NS	
Myocardial Infarction (D)	NS	ns	NS	ns	
Stroke or Transient Ischemic Attack (D)	NS	NS	--	NS	
Physical Examination					
Systolic Blood Pressure (C)	ns	ns	NS	ns	
Systolic Blood Pressure (D)	ns	ns	NS	ns	
Diastolic Blood Pressure (C)	NS	ns	NS	NS	
Diastolic Blood Pressure (D)	NS	NS	NS	ns	
Heart Sounds (D)	ns	ns	ns	ns	
Overall Electrocardiograph (ECG) (D)	ns	NS	NS	ns*	
ECG: Right Bundle Branch Block (D)	ns	ns	NS	ns	
ECG: Left Bundle Branch Block (D)	ns	ns	--	ns	
ECG: Non-Specific ST- and T-Wave Changes (D)	NS	NS	NS	ns	
ECG: Bradycardia (D)	ns	ns	NS	ns	
ECG: Tachycardia (D)	NS	--	--	NS	
ECG: Arrhythmia (D)	NS	NS	NS	ns	
ECG: Evidence of Prior Myocardial Infarction (D)	ns	ns	NS	ns	
ECG: Other Diagnoses (D)	NS	--	--	NS	
Funduscopic Examination (D)	ns	NS	NS	-0.047	
Carotid Bruits (D)	ns	ns	NS	ns	
Radial Pulses (D)	NS	NS	--	NS	
Femoral Pulses (D)	NS	NS	NS	NS	
Popliteal Pulses (D)	NS	ns	ns	NS	
Dorsalis Pedis Pulses (D)	ns	NS	NS	ns	
Posterior Tibial Pulses (D)	NS	NS	NS	NS	
Leg Pulses (D)	NS	NS	NS	ns	
Peripheral Pulses (D)	NS	NS	NS	ns	
Self-reported Questionnaire					
Intermittent Claudication and Vascular Insufficiency Index (ICVI) (D)	ns	NS	ns	NS	

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

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

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk ≥ 1.00 .

-: Relative risk < 1.00 .

--: Analysis not performed because of the sparse number of participants with an abnormality.

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

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 a relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

14.4.2 Model 2: Initial Dioxin Analysis

Model 2 analyses revealed a significant positive association between initial dioxin and evidence of prior myocardial infarction from the ECG. The results of all unadjusted and adjusted Model 2 analyses are summarized in Table 14-40.

Table 14-40. Summary of Initial Dioxin Analysis (Model 2) for Cardiovascular Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Medical Records		
Essential Hypertension (D)	NS	NS
Heart Disease (Excluding Essential Hypertension) (D)	-0.001	ns
Myocardial Infarction (D)	NS	NS
Stroke or Transient Ischemic Attack (D)	NS	NS
Physical Examination		
Systolic Blood Pressure (C)	ns	ns
Systolic Blood Pressure (D)	-0.031	ns
Diastolic Blood Pressure (C)	NS	NS
Diastolic Blood Pressure (D)	NS	NS
Heart Sounds (D)	NS	NS
Overall Electrocardiograph (ECG) (D)	ns	NS
ECG: Right Bundle Branch Block (D)	ns	NS
ECG: Left Bundle Branch Block (D)	ns	--
ECG: Non-Specific ST- and T-Wave Changes (D)	ns	NS
ECG: Bradycardia (D)	ns	ns
ECG: Tachycardia (D)	NS	--
ECG: Arrhythmia (D)	ns	NS
ECG: Evidence of Prior Myocardial Infarction (D)	NS	+0.012
ECG: Other Diagnoses (D)	NS	--
Funduscopic Examination (D)	ns	NS
Carotid Bruits (D)	NS	NS
Radial Pulses (D)	ns	--
Femoral Pulses (D)	ns	NS
Popliteal Pulses (D)	ns	ns
Dorsalis Pedis Pulses (D)	ns	NS
Posterior Tibial Pulses (D)	NS	NS
Leg Pulses (D)	ns	NS
Peripheral Pulses (D)	ns	NS
Self-reported Questionnaire		
Intermittent Claudication and Vascular Insufficiency Index (ICVI) (D)	ns	NS

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

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk ≥ 1.00 .

-: Relative risk <1.00 .

--: Analysis not performed because of the sparse number of Ranch Hands with an abnormality.

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

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 a relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

14.4.3 Model 3: Categorized Dioxin Analysis

The adjusted Model 3 analysis revealed a significantly higher occurrence of heart disease for Ranch Hands in the background dioxin category than for Comparisons. A significantly lower prevalence of abnormal heart sounds was found for Ranch Hands in the background dioxin category than for Comparisons. The percentage of Ranch Hands in the low dioxin category with a history of heart disease was marginally significantly greater than Comparisons. The prevalence of Ranch Hands in the low dioxin category with abnormal ECG findings was marginally significantly smaller than Comparisons. Ranch Hands in the high dioxin category had a significantly greater prevalence of tachycardia and other ECG diagnoses than Comparisons. The results of all unadjusted and adjusted Model 3 analyses are summarized in Table 14-41.

Table 14-41. Summary of Categorized Dioxin Analysis (Model 3) for Cardiovascular 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
Medical Records				
Essential Hypertension (D)	ns	ns	NS	NS
Heart Disease (Excluding Essential Hypertension) (D)	+0.005	+0.011	ns	ns
Myocardial Infarction (D)	ns	ns	NS	NS
Stroke or Transient Ischemic Attack (D)	NS	ns	NS	ns
Physical Examination				
Systolic Blood Pressure (C)	ns	NS	ns*	ns
Systolic Blood Pressure (D)	NS	NS	ns	ns
Diastolic Blood Pressure (C)	ns	ns	NS*	NS
Diastolic Blood Pressure (D)	ns	NS	NS	NS
Heart Sounds (D)	-0.047	ns	ns	ns
Overall Electrocardiograph (ECG) (D)	NS	ns	ns	ns
ECG: Right Bundle Branch Block (D)	ns	ns	NS	ns
ECG: Left Bundle Branch Block (D)	NS	ns	ns	ns
ECG: Non-Specific ST- and T-Wave Changes (D)	ns	NS	NS	NS
ECG: Bradycardia (D)	ns	ns	-0.042	-0.020
ECG: Tachycardia (D)	NS	ns	+0.033	NS
ECG: Arrhythmia (D)	ns	NS	ns	NS
ECG: Evidence of Prior Myocardial Infarction (D)	ns	NS	ns	ns
ECG: Other Diagnoses (D)	NS	ns	+0.042	NS
Funduscopic Examination (D)	ns	NS	ns	NS
Carotid Bruits (D)	ns	ns	NS	NS
Radial Pulses (D)	NS	NS	NS	NS
Femoral Pulses (D)	NS	NS	NS	NS*
Popliteal Pulses (D)	ns	NS	NS	NS
Dorsalis Pedis Pulses (D)	ns	NS	ns	NS
Posterior Tibial Pulses (D)	NS	NS	NS	NS
Leg Pulses (D)	ns	NS	NS	NS
Peripheral Pulses (D)	ns	NS	NS	NS

Table 14-41. Summary of Categorized Dioxin Analysis (Model 3) for Cardiovascular Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	Background Ranch Hands vs. Comparisons	UNADJUSTED			
		Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons	
Self-reported Questionnaire					
Intermittent Claudication and Vascular Insufficiency Index (ICVI) (D)	ns	NS	NS	NS	NS

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

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

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk ≥ 1.00 .

-: Relative risk < 1.00 .

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

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 a relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

Variable	Background Ranch Hands vs. Comparisons	ADJUSTED			
		Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons	
Medical Records					
Essential Hypertension (D)	ns	ns	NS	NS	NS
Heart Disease (Excluding Essential Hypertension) (D)	+0.032	NS*	NS	NS	NS
Myocardial Infarction (D)	ns	ns	NS	NS	NS
Stroke or Transient Ischemic Attack (D)	ns	ns	NS	NS	NS
Physical Examination					
Systolic Blood Pressure (C)	NS	ns	ns	ns	ns
Systolic Blood Pressure (D)	NS	NS	ns	ns	ns
Diastolic Blood Pressure (C)	ns	ns	NS	NS	NS
Diastolic Blood Pressure (D)	ns	ns	NS	NS	NS
Heart Sounds (D)	-0.041	ns	NS	ns	ns
Overall Electrocardiograph (ECG) (D)	NS	ns*	NS	ns	ns
ECG: Right Bundle Branch Block (D)	NS	ns	NS	ns	ns
ECG: Left Bundle Branch Block (D)	ns	ns	--	--	--
ECG: Non-Specific ST- and T-Wave Changes (D)	ns	ns	NS	NS	NS
ECG: Bradycardia (D)	ns	ns	ns	ns*	ns*
ECG: Tachycardia (D)	NS	--	+0.032	--	--
ECG: Arrhythmia (D)	ns	NS	NS	NS	NS
ECG: Evidence of Prior Myocardial Infarction (D)	ns	ns	NS	ns	ns
ECG: Other Diagnoses (D)	NS	--	+0.050	--	--
Funduscopic Examination (D)	NS	ns	ns	ns	ns
Carotid Bruits (D)	NS	ns	NS	ns	ns
Radial Pulses (D)	NS	NS	NS	NS	NS
Femoral Pulses (D)	NS	NS	NS	NS	NS

Table 14-41. Summary of Categorized Dioxin Analysis (Model 3) for Cardiovascular 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
Popliteal Pulses (D)	ns	NS	NS	NS
Dorsalis Pedis Pulses (D)	ns	ns	ns	ns
Posterior Tibial Pulses (D)	NS	NS	NS	NS
Leg Pulses (D)	NS	NS	ns	ns
Peripheral Pulses (D)	NS	NS	ns	NS
Self-reported Questionnaire				
Intermittent Claudication and Vascular Insufficiency Index (ICVI) (D)	ns	ns	NS	NS

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

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

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk ≥ 1.00 .

-: Relative risk < 1.00 .

--: Analysis not performed because of the sparse number of participants with an abnormality.

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

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 a relative risk less than 1.00 for discrete analysis or difference of means negative for continuous analysis.

14.4.4 Model 4: 1987 Dioxin Level Analysis

The adjusted Model 4 analysis revealed a significant positive association between essential hypertension and 1987 dioxin. A marginally significant association between the evidence of a prior myocardial infarction, as determined from the ECG, and 1987 dioxin also was observed. The results of all unadjusted and adjusted Model 4 analyses are summarized in Table 14-42.

Table 14-42. Summary of 1987 Dioxin Analysis (Model 4) for Cardiovascular Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Medical Records		
Essential Hypertension (D)	+<0.001	+0.011
Heart Disease (Excluding Essential Hypertension) (D)	-0.004	ns
Myocardial Infarction (D)	NS	NS
Stroke or Transient Ischemic Attack (D)	ns	NS
Physical Examination		
Systolic Blood Pressure (C)	NS	ns
Systolic Blood Pressure (D)	NS	ns*
Diastolic Blood Pressure (C)	+0.014	NS
Diastolic Blood Pressure (D)	NS	NS

Table 14-42. Summary of 1987 Dioxin Analysis (Model 4) for Cardiovascular Variables (Ranch Hands Only) (Continued)

Variable	Unadjusted	Adjusted
Heart Sounds (D)	NS	NS
Overall Electrocardiograph (ECG) (D)	ns	NS
ECG: Right Bundle Branch Block (D)	NS	NS
ECG: Left Bundle Branch Block (D)	ns	ns
ECG: Non-Specific ST- and T-Wave Changes (D)	NS	NS
ECG: Bradycardia (D)	ns*	ns
ECG: Tachycardia (D)	NS	NS
ECG: Arrhythmia (D)	ns	NS
ECG: Evidence of Prior Myocardial Infarction (D)	NS	NS*
ECG: Other Diagnoses (D)	NS	NS
Funduscopic Examination (D)	NS	NS
Carotid Bruits (D)	NS	ns
Radial Pulses (D)	ns	ns
Femoral Pulses (D)	NS	NS
Popliteal Pulses (D)	ns	NS
Dorsalis Pedis Pulses (D)	ns	NS
Posterior Tibial Pulses (D)	NS	NS
Leg Pulses (D)	NS	NS
Peripheral Pulses (D)	NS	NS
Self-reported Questionnaire		
Intermittent Claudication and Vascular Insufficiency Index (ICVI) (D)	NS	NS

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

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

C: Continuous analysis.

D: Discrete analysis.

+: Relative risk ≥ 1.00 for discrete analysis; slope nonnegative for continuous analysis.

-: Relative risk < 1.00 .

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

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 a relative risk less than 1.00 for discrete analysis or slope negative for continuous analysis.

14.5 CONCLUSION

Analyses revealed that Ranch Hands had a significantly higher percentage of participants with a history of heart disease (excluding essential hypertension) than did Comparisons and, in particular, within enlisted flyers. However, the risk of disease was not significantly increased in Ranch Hand enlisted groundcrew—the military occupation with the highest dioxin levels. The association between heart disease and initial dioxin for Ranch Hands showed a negative dose-response trend, with heart disease decreasing as initial dioxin increased. Furthermore, Ranch Hands in the background and the low dioxin categories had more heart disease than did Comparisons, but this increase was not seen in Ranch Hands in the high dioxin category. Increases in tachycardia and other ECG findings, such as pre-excitation, were seen for Ranch Hands in the high dioxin category, although the analyses were based on a sparse number of abnormalities. A significant positive association between initial dioxin and evidence of prior myocardial infarction from the ECG was observed in Ranch Hands, and a marginally significant positive

association was observed between 1987 dioxin and evidence of prior myocardial infarction from the ECG. A positive association between 1987 dioxin and essential hypertension also was observed in Ranch Hands. In contrast to previous AFHS examinations, no relation was found between peripheral pulses and any measures of exposure.

In summary, in contrast to prior examinations, the current study has documented that Ranch Hands are more likely than Comparisons to have historical evidence for heart disease (excluding essential hypertension) but are no longer at greater risk for the occurrence of pulse deficits. By all other indices, the prevalence of cardiovascular disease appears similar in both cohorts. For the first time, there is evidence that levels of dioxin may be a risk factor for the development of essential hypertension and prior myocardial infarction as indicated by interpretation of the ECG. As of 1997, the verified history of essential hypertension was associated with 1987 dioxin, and the evidence of prior myocardial infarction from the ECG was associated with initial dioxin. These findings, in conjunction with the increase in the number of deaths caused by diseases of the circulatory system for Ranch Hand nonflying enlisted personnel based on the 1994 AFHS mortality update (34), showed associations with dioxin that require further observation. A biological mechanism for the relation between dioxin and heart disease is unknown at this time.

REFERENCES

1. Hermansky, S. J., T. L. Holcslaw, W. J. Murray, R. S. Markin, and S. J. Stohs. 1988. Biochemical and functional effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the heart of female rats. *Toxicology and Applied Pharmacology* 95:175-84.
2. Canga, L., R. Levi, and A. B. Rifkind. 1988. Heart as a target organ in 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity: Decreased beta-adrenergic responsiveness and evidence of increased intracellular calcium. *Proceedings of the National Academy of Sciences* 85:905-9.
3. Kelling, C. K., L. A. Menahan, and R. E. Peterson. 1987. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin treatment on mechanical function of the rat heart. *Toxicology and Applied Pharmacology* 91:497-501.
4. Brewster, D. W., F. Matsumura, and T. Akera. 1987. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on guinea pig heart muscle. *Toxicology and Applied Pharmacology* 89:408-17.
5. Brewster, D. W., D. W. Bommbick, and F. Matsumura. 1988. Rabbit serum hypertriglyceridemia after administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Journal of Toxicology and Environmental Health* 25:495-507.
6. Brewster, D. W., and F. Matsumura. 1989. Differential effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on adipose tissue lipoprotein lipase activity in the guinea pig, rat, hamster, rabbit, and mink. *Comparative Biochemistry and Physiology* 93C:49-53.
7. Kociba, R. J., D. G. Keyes, J. E. Beyer, R. M. Carreon, C. E. Wade, D. A. Dittenber, R. P. Kalnins, L. E. Frauson, C. N. Park, S. D. Barnard, R. A. Hummel, and C. G. Humiston. 1978. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. *Toxicology and Applied Pharmacology* 46:279-303.
8. Cantrell, S. M., L. H. Lutz, D. E. Tillitt, and M. Hannink. 1996. Embryotoxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD): The embryonic vasculature is a physiological target to TCDD-induced DNA damage and apoptotic cell death in Medaka (*Orizias latipes*). *Toxicology and Applied Pharmacology* 141:23.
9. Guiney, P. D., R. M. Smolowitz, R. E. Peterson, and J. J. Stegeman. 1997. Correlation of 2,3,7,8-tetrachlorodibenzo-p-dioxin induction of cytochrome P4501A in vascular endothelium with toxicity in early life stages of lake trout. *Toxicology and Applied Pharmacology* 143:256.
10. Schiller, C. M., C. M. Adcock, and R. A. Moore. 1985. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin and fasting on body weight and lipid parameters in rats. *Toxicology and Applied Pharmacology* 81:356-61.
11. Jovanovich, L., S. Levin, and M. Kahn. 1987. Significance of mirex-caused hypoglycemia and hyperlipidemia in rats. *Journal of Biochemistry and Toxicology* 2:203-13.
12. Swift, L. L., T. A. Gasiewicz, and G. D. Dunn. 1981. Characterization of the hyperlipidemia in guinea pigs induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicology and Applied Pharmacology* 59:489-99.
13. Moses, M., R. Lillis, K. D. Crow, J. Thornton, A. Fischbein, H. A. Anderson, and I. J. Selikoff. 1984. Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: Comparison of findings with and without chloracne. *American Journal of Industrial Medicine* 5:161-82.

14. Suskind, R. R., and V. S. Hertzberg. 1984. Human health effects of 2,4,5-T and its toxic contaminants. *Journal of the American Medical Association* 251:2372-80.
15. Zack, J. A., and W. R. Gaffey. 1983. A mortality study of workers employed at the Monsanto company plant in Nitro, West Virginia. *Environmental Science Research* 26:575-91.
16. Bond, G. G., M. G. Ott, F. E. Brenner, and R. R. Cook. 1983. Medical and morbidity surveillance findings among employees potentially exposed to TCDD. *British Journal of Industrial Medicine* 40:318-24.
17. Von Benner, A., L. Edler, K. Mayer, and A. Zober. 1994. 'Dioxin' investigation program of the chemical industry professional association. *Arbeitsmedizin Sozialmedizin Präventivmedizin* 29:11-6.
18. Bertazzi, P. A., C. Zocchetti, A. C. Pesatori, S. Guercilena, M. Sanarico, and L. Radice. 1989. Mortality in an area contaminated by TCDD following an industrial incident. *Medicina del Lavoro (Italy)* 80:316-29.
19. Bertazzi, P. A., C. Zocchetti, A. C. Pesatori, S. Guercilena, M. Sanarico, and L. Radice. 1989. Ten-year mortality study of the population involved in the Seveso incident in 1976. *American Journal of Epidemiology* 129:1187-200.
20. Zack, J. A., and R. R. Suskind. 1980. The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol process accident. *Journal of Occupational Medicine* 22:11-4.
21. Zober, A., M. G. Ott, and P. Messerer. 1994. Morbidity follow-up study of BASF employees exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after a 1953 chemical reactor incident. *Occupational and Environmental Medicine* 51:469-86.
22. Ott, M. G., A. Zober, and C. Germann. 1994. Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD. *Chemosphere* 29:2423-37.
23. Kogan, M. D., and R. W. Clapp. 1985. Mortality among Vietnam veterans in Massachusetts, 1972-1983. Massachusetts Office of the Commissioner of Veterans Services, Agent Orange Program.
24. Fett, M. J., J. R. Nairn, D. M. Cobbin, and M. A. Adena. 1987. Mortality among Australian conscripts of the Vietnam conflict era. II. Causes of death. *American Journal of Epidemiology* 125:878-84.
25. Anderson, H. A., L. P. Hanrahan, M. Jensen, D. Laurin, W.-Y. Yick, and P. Wiegman. 1986. Wisconsin Vietnam veteran mortality study: proportionate mortality ratio study results. Madison: Wisconsin Division of Health.
26. Centers for Disease Control (CDC). 1987. Postservice mortality among Vietnam veterans. *Journal of the American Medical Association* 257:790-5.
27. Centers for Disease Control. 1988. Health status of Vietnam veterans. II. Physical health. *Journal of the American Medical Association* 259:2708-14.
28. Pollei, S., F. A. Mettler Jr., C. A. Kelsey, M. R. Walters, and R. E. White. 1986. Follow-up chest radiographs in Vietnam veterans: Are they useful? *Radiology* 161:101-2.
29. Watanabe, K. K., H. K. Kang, and T. L. Thomas. 1991. Mortality among Vietnam veterans: with methodological considerations. *Journal of Occupational Medicine* 33:780-5.
30. Thomas, T. L., and H. K. Kang. 1990. Mortality and morbidity among Army Chemical Corps Vietnam veterans: a preliminary report. *American Journal of Industrial Medicine* 18:665-73.

31. Thomas, T. L., H. Kang, and N. Dalager. 1991. Mortality among women Vietnam veterans, 1973-1987. *American Journal of Epidemiology* 134:973-80.
32. Eisen, S., J. Goldberg, W. R. True, and W. G. Henderson. 1991. A co-twin control study of the effects of the Vietnam war on the self-reported physical health of veterans. *American Journal of Epidemiology* 134:49-59.
33. Stellman, S. D., J. M. Stellman, and J. F. Sommer, Jr. 1988. Health and reproductive outcomes among American Legionnaires in relation to combat and herbicide exposure in Vietnam. *Environmental Research* 47:150-74.
34. Roegner, R. H., W. D. Grubbs, M. B. Lustik, A. S. Brockman, S. C. Henderson, D. E. Williams, W. H. Wolfe, J. E. Michalek, and J. C. Miner. 1991. The Air Force Health Study: An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides. Serum dioxin analysis of 1987 examination results. NTIS: AD A 237 516-24. United States Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas.
35. Grubbs, W. D., W. H. Wolfe, J. E. Michalek, D. E. Williams, M. B. Lustik, A. S. Brockman, S. C. Henderson, F. R. Burnett, R. G. Land, D. J. Osborne, V. K. Rocconi, M. E. Schreiber, J. C. Miner, G. L. Henriksen, and J. A. Swaby. 1995. The Air Force Health Study: An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: Final Report. 1992 Followup Examination Results. NTIS: AD A 304 306, 304 308-316. United States Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas.
36. Wolfe, W. H., J. E. Michalek, and J. C. Miner. 1994. The Air Force Health Study: An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: Mortality update - 1994. Epidemiologic Research Division, Armstrong Laboratory, Human Systems Center, Brooks Air Force Base, Texas.
37. Flesch-Janys, D., J. Berger, P. Gurn, A. Manz, S. Nagel, H. Waltsgott, and J. H. Dwyer. 1995. Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. *American Journal of Epidemiology* 142(11):1165-75.
38. Henriksen, G. L., N. S. Ketchum, J. E. Michalek, and J. A. Swaby. 1997. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. *Epidemiology* 8:252-8.
39. Assennato, G., D. Cervino, E. A. Emmett, G. Longo, and F. Merlo. 1989. Follow-up of subjects who developed chloracne following TCDD exposure at Seveso. *American Journal of Industrial Medicine* 16:119-25.
40. Fingerhut, M. A., W. E. Halperin, D. A. Marlow, L. A. Piacitelli, P. A. Honchar, M. H. Sweeney, A. L. Greife, P. A. Dill, K. Steenland, and A. J. Suruda. 1991. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *New England Journal of Medicine* 324(4):212-8.
41. Martin, J. V. 1984. Lipid abnormalities in workers exposed to dioxin. *British Journal of Industrial Medicine* 41:254-6.
42. Ashe, W. F., and R. R. Siskind. 1982. Progress report - patients from Monsanto Chemical company, Nitro, West Virginia, 1959. Quoted by Hay, AWM in: *The chemical scythe: lessons of 2,4,5-T and dioxin*. New York and London: Plenum Press.
43. Oliver, R. M. 1975. Toxic effects of 2,3,7,8-tetrachlorodibenzo 1,4-dioxin on laboratory workers. *British Journal of Industrial Medicine* 32:49-53.
44. Walker, A. E., and J. V. Martin. 1979. Lipid profiles in dioxin exposed workers. *Lancet* i:446-7.

45. Lathrop, G. D., W. H. Wolfe, R. A. Albanese, and P. M. Moynahan. 1984. The Air Force Health Study: An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: Baseline Morbidity Study Results. NTIS: AD A-138-340. United States Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas.
46. Wolfe, W. H., J. E. Michalek, J. C. Miner, A. Rahe, J. Silva, W. F. Thomas, W. D. Grubbs, M. B. Lustik, T. G. Garrison, R. H. Roegner, and D. E. Williams. 1990. Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical health. *Journal of the American Medical Association* 264:1824-31.
47. Hoffman, R. E., P. A. Stehr-Green, K. B. Webb, G. Evans, A. P. Knutsen, W. F. Schramm, J. L. Staake, B. B. Gibson, and K. K. Steinberg. 1986. Health effects of long-term exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Journal of the American Medical Association* 255:2031-38.
48. Stehr, P. A., G. Stein, H. Falk, E. Sampson, S. J. Smith, K. Steinberg, K. Webb, S. Ayres, and W. Schramm. 1986. A pilot epidemiologic study of possible health effects associated with 2,3,7,8-tetrachlorodibenzo-p-dioxin contamination in Missouri. *Archives of Environmental Health* 41:16-22.
49. Lathrop, G. D., S. G. Machado, T. G. Garrison, W. D. Grubbs, W. F. Thomas, W. H. Wolfe, J. E. Michalek, J. C. Miner, and M. R. Peterson. 1987. The Air Force Health Study: An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: First followup examination results. NTIS: AD A 188262. United States Air Force School of Aerospace Medicine. Brooks Air Force Base, Texas.
50. Knapik, J. J., A. R. L. Burse, and J. A. Vogel. 1983. Height, weight, percent body fat, and indices of adiposity for young men and women entering the Army. *Aviation, Space, and Environmental Medicine* 54:223-31.
51. Jenkins, C. D., R. H. Roseman, and S. J. Zyzanski. 1974. Prediction of clinical coronary heart disease by a test for the coronary-prone behavior pattern. *New England Journal of Medicine* 290(23):1271-5.
52. Michalek, J. E., J. L. Pirkle, S. P. Caudill, R. C. Tripathi, D. G. Patterson Jr., and L. L. Needham. 1996. Pharmacokinetics of TCDD in Veterans of Operation Ranch Hand: 10-year Followup. *Journal of Toxicology and Environmental Health* 47:209-20.
53. Mausner, J. S., and A. K. Bahn. 1974. *Epidemiology - An Introductory Text*. Philadelphia: W. B. Saunders Company.

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15 HEMATOLOGIC ASSESSMENT

15.1 INTRODUCTION

15.1.1 Background

Experiments in laboratory animals have demonstrated that 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) is directly toxic to the hematopoietic system in several species. In one study, dioxin administered in low doses (0.70 µg/kg or 350 µg/kg of dioxin by oral gavage) to monkeys resulted in elevated neutrophil counts while higher doses were associated with lympho- and thrombocytopenia (1). A decrease in overall cellularity and an increase in the myeloid-erythroid ratio were noted in approximately half of the sternal bone marrow samples examined at the conclusion of the experiment.

Other animal studies have shown that the toxic effects of dioxin on the hematopoietic system vary depending on the dose employed and the species examined. In many reports, it is difficult to distinguish primary effects from those occurring secondary to systemic toxicity. One study in rats using gavage doses of dioxin varying from 0.001 to 1.0 µg/kg noted depressed red blood cell (RBC) counts and packed cell volumes in the high-dose group (2). In another rat experiment employing 10 µg/kg of dioxin orally, elevated erythrocyte, reticulocyte, and neutrophil counts were noted with reduction in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelet counts, and clot retraction times—effects that the authors felt could be attributed to systemic toxicity with terminal dehydration (3). In a multispecies study, mice and guinea pigs given oral doses of dioxin varying from 0.1 µg/kg to 50 µg/kg were found to have dose-dependent reductions in leukocytes with relative lymphocytopenia within 1 week of dioxin administration, and thrombocytopenia and hemoconcentration were found in rats (4).

Several animal experiments, although designed primarily to investigate immunologic sequelae of dioxin exposure, have focused on selected hematologic elements, particularly macrophages and polymorphonuclear leukocytes, but whether the responses observed were secondary to inflammation or specific to dioxin is not known (3, 5–7).

More recent animal research relevant to the hematopoietic system has focused on the altered cellular differentiation associated with dioxin toxicity. In mice, progenitor cells were suppressed following exposure to dioxin in doses as low as 1.0 µg/kg of body weight, and *in vitro* studies demonstrated that myelotoxicity occurs by a direct inhibition of proliferating stem cells (8). A subsequent study from the same laboratory demonstrated a direct effect of dioxin on cultured lymphocytes resulting in a selective inhibition of B-cell differentiation into antibody-secreting cells (9). In these and other studies (10), the authors cite evidence for the role of the aryl hydrocarbon (Ah) receptor in mediating these myelo- and lymphotoxic effects. In another report, the presence of the Ah receptor was defined in the spleens of numerous primate species (11). Although Ah receptors have been isolated in the tissue of several human organs (12–17), the relevance of these observations to dioxin hematopoietic toxicity remains to be proven (18).

In general, human observational studies have shown fewer and less consistent hematologic findings than the structured animal experiments. Mortality and morbidity studies that have included hematologic data as endpoints have been based on populations exposed to dioxin by occupation (19–21), environmental contamination (22–26), consequent to industrial chemical accidents (27–33), and during military service in Southeast Asia (SEA) (34–39).

In the cancer mortality study reported by the National Institute of Occupational Safety and Health, one of few to incorporate serum dioxin data into the analyses, there was no significant increase in the relative risk of hematologic malignancies associated with exposure to dioxin in either the entire cohort or in a subcohort with more than 20 years of latency (19). Numerous studies have been conducted on cohorts that were exposed to dioxin by contamination of soil at the Quail Run (22–24) and Times Beach (25) residential areas of Missouri. With one exception, no differences were found in any of the hematologic parameters examined. In the Times Beach study, a statistically significant increase in the mean platelet count was noted in the exposed cohort relative to the unexposed, but the difference (281,927 mm³ vs. 249,061 mm³) was not considered clinically meaningful. A follow-up study, the first to report clinical hematologic indices in relation to tissue levels of dioxin (26), found no abnormalities in the complete blood count related to the body burden of dioxin.

A clinical epidemiological study was conducted 30 years after an explosion in a trichlorophenol plant in Nitro, West Virginia. The study compared 204 highly exposed employees, 86 percent of whom had developed chloracne, with 163 employees who were not exposed (27). No significant differences were found in the standard hematologic indices. A recent mortality experience study of 754 workers employed at the same plant, 122 of whom had sufficiently severe dioxin exposure to cause chloracne, found no increased mortality associated with all lymphatic and hematopoietic malignancies (32).

The monitoring of the populations heavily exposed to dioxin during the Seveso, Italy, hexachlorophene manufacturing plant explosion in 1976 and at the BASF chemical plant in 1953 continues to generate reports of medical surveillance. Although transient depression of the peripheral white blood cell (WBC) count after dioxin exposure has been documented (20, 21), a morbidity study of workers involved in the cleanup of the Seveso environs found no differences in selected hematologic indices (hemoglobin, WBC count, and platelets) between exposed subjects and controls (33). In the most recent report on the BASF population, exposed subjects had a significantly higher erythrocyte sedimentation rate than referents (6.53 mm/hr vs. 4.95 mm/hr), but no differences were noted in the WBC count, platelet count, or hemoglobin (20).

In previous reports of the Air Force Health Study (AFHS) (35–37), Ranch Hand participants were found to have slightly higher mean platelet counts than Comparisons and, in the 1987 follow-up examinations (37), a significantly greater percentage of abnormally high platelet counts as well. In the serum dioxin analysis of the 1987 examinations (38), Ranch Hands with the highest current serum dioxin levels had higher mean platelet and total WBC counts than Comparisons, results that raised the possibility of a chronic inflammatory response associated with dioxin levels. In the 1992 examinations, when the results were adjusted for covariates, no significant group differences were noted between the Ranch Hand and Comparison cohorts, nor was there any evidence for a persistent inflammatory response related to prior exposure to dioxin (39).

15.1.2 Summary of Previous Analyses of the Air Force Health Study

15.1.2.1 1982 Baseline Study Summary Results

The functional integrity of the hematopoietic system was assessed at the 1982 baseline examination by the measurement of eight peripheral blood variables: RBC count, WBC count, hemoglobin, hematocrit, MCV, MCH, mean corpuscular hemoglobin concentration (MCHC), and platelet count. These variables were analyzed in the discrete form to detect differences in the percentages of values outside the designed laboratory range, as well as analyzed in the continuous form to detect shifts in mean values between the Ranch Hand and Comparison groups.

The Ranch Hand group had a significantly higher adjusted mean MCV and MCH than the Comparison group ($p=0.05$ and $p=0.04$, respectively), although the magnitude of the difference was small in each case. The Ranch Hand adjusted mean values for five other parameters (i.e., RBC, WBC, hemoglobin, hematocrit, and MCHC) were nearly identical to the adjusted mean values of the Comparison group. The mean platelet count for Ranch Hands was marginally significantly greater than the Comparison mean count ($p=0.06$). The percent of abnormal values for these eight variables, as established by the upper and lower limits of normal, did not differ significantly between the two groups.

15.1.2.2 1985 Follow-up Study Summary Results

The same eight peripheral blood variables (i.e., RBC, WBC, hemoglobin, hematocrit, MCV, MCH, MCHC, and platelet count) were analyzed in the 1985 follow-up study. The unadjusted discrete analysis of the percent abnormal values, both low and high, showed no statistically significant difference between the Ranch Hand and Comparison groups for any of the hematologic variables. Similarly, in the adjusted discrete analyses, none of the adjusted relative risks was significant.

As no subgroup demonstrated consistent patterns of hematologic impairment, biologic relevance was not assigned to the interactions. The significant group differences found for MCV and MCH at the baseline examination were not present in the 1985 follow-up analyses. The covariate effects of age, race, occupation, and lifetime smoking history were highly significant for many of the hematologic variables.

The longitudinal analyses of MCV, MCH, and platelet count found a significant group difference for platelet count, with the Ranch Hands having an average decrease in platelet count between examinations and the Comparisons having an average increase. As a result, the baseline group difference (nonsignificant) in mean values approached equality at the 1985 follow-up examination.

In conclusion, none of the eight hematologic variable means was found to differ significantly between the Ranch Hand and Comparison groups. The expected effects of age, race, and smoking were demonstrated with most of the hematologic variables. The longitudinal analyses also suggested that neither group manifested an impairment of the hematopoietic system. Exposure index analyses did not support a plausible dose-response relation for any of the hematologic variables.

15.1.2.3 1987 Follow-up Study Summary Results

The hematologic status of the Ranch Hand and Comparison groups was assessed by the examination of the same eight variables used in the two previous examinations: RBC, WBC, hemoglobin, hematocrit, MCV, MCH, MCHC, and platelet count. There were no statistically significant differences between the Ranch Hand and Comparison groups for mean RBC count, hemoglobin, hematocrit, MCV, MCH, and MCHC, in analyses either unadjusted or adjusted for the covariates of age, race, occupation, current cigarette smoking, and lifetime cigarette smoking history. For WBC count, the unadjusted mean level was significantly greater in Ranch Hands than in Comparisons. The difference was not statistically significant after adjustment for covariates, nor were significant differences detected in the percentage of individuals with abnormal values.

Mean platelet counts also were significantly greater in Ranch Hands than in Comparisons, as was the percentage of individuals with abnormally high platelet counts. Longitudinal analyses detected a significantly greater decrease in the mean platelet count in Ranch Hands than in Comparisons, despite the higher overall mean count, from the baseline examination to the 1987 follow-up examination.

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

The number of dependent hematologic variables was increased from eight to nine with the addition of prothrombin time. Several of the nine variables showed an association with initial dioxin in the unadjusted model, but when the model was adjusted for covariates, the associations became nonsignificant. Hemoglobin and hematocrit were positively associated with current dioxin when time since duty in SEA was no more than 18.6 years and negatively associated with current dioxin when time since duty in SEA was greater than 18.6 years. For the discrete RBC count analysis, the relative risk of an abnormally low count was less than one when time since duty in SEA did not exceed 18.6 years and was greater than one when time since duty in SEA was more than 18.6 years. Because a low RBC count was considered abnormal for the purpose of these statistical analyses, the trend in relation to current dioxin was similar to that in the continuous analyses of hemoglobin and hematocrit. In the discrete analysis of prothrombin time, the trend in relation to current dioxin also was similar to that in the continuous analyses of hemoglobin and hematocrit. In the categorized current dioxin analyses, whenever the overall contrast showed significant, or marginally significant, differences among the categories, the mean level or percent abnormal in the three categories of Ranch Hands (i.e., officers, enlisted flyers, and enlisted groundcrew) tended to exceed the corresponding mean level or percent abnormal in the background category that consisted of Comparisons. The longitudinal analyses of MCV, MCH, and platelet count displayed no significant associations with dioxin.

In summary, the results of the previous analysis revealed no meaningful association between hematopoietic toxicity and dioxin exposure. Statistical analyses of two variables (WBC and platelet count) raised the possibility of subtle biologic effects that cannot be considered clinically meaningful but did point to the need for follow-up in future AFHS examinations. The increased platelet and WBC counts, in addition to the elevation of erythrocyte sedimentation rates (in the general health assessment), were thought to indicate the presence of a chronic inflammatory response to dioxin exposure.

15.1.2.5 1992 Follow-up Study Summary Results

The number of dependent hematologic variables was increased from 9 to 13 with elimination of MCV, MCH, and MCHC and the addition of RBC morphology (normal, abnormal), absolute neutrophils (segs), absolute neutrophils (bands), absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils. The 13 endpoints analyzed in the hematology assessment provided a comprehensive evaluation of the three peripheral blood lines (erythrocytes, leukocytes, and platelets) and their relation to dioxin exposure. In the analyses of these variables, only platelet count exhibited significant associations with the herbicide exposure indices. Ranch Hands in the enlisted flyer and enlisted groundcrew categories possessed statistically significant higher mean platelet counts than Comparisons, although the result was not considered meaningful from a clinical point of view. Analyses using extrapolated levels of initial dioxin showed that Ranch Hands with high dioxin levels had significantly greater mean platelet count measurements than Comparisons. Platelet counts also were positively associated with current serum dioxin measurements, although the association became nonsignificant when adjusted for covariates. The 1992 follow-up results supported the results found in both the 1987 follow-up study and in the serum dioxin analysis of the 1987 follow-up study, but the biologic meaning was uncertain. Results from the 1987 follow-up study generated questions regarding the possibility of a subclinical inflammatory response associated with prior dioxin exposure. This was due to elevated mean WBC counts, platelet counts, and erythrocyte sedimentation rates in Ranch Hands. The 1992 follow-up study did not produce significant results to support this possibility. Therefore, in conclusion, there was no evidence from the 1992 follow-up study that suggested an association between hematopoietic toxicity and prior dioxin exposure.

15.1.3 Parameters for the 1997 Hematologic Assessment

15.1.3.1 Dependent Variables

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

15.1.3.1.1 Laboratory Examination Data

A total of 13 hematology variables measured at the laboratory as part of the 1997 follow-up examination were analyzed statistically. These variables were the same as those studied in 1992 and included five cell counts, one RBC morphology, six measures of absolute blood counts, and a coagulation measure (prothrombin time). These variables were determined by routine hematologic procedures. In particular, the cell count indices were performed on the Coulter STKS® automated instrument, and prothrombin time was measured on the AMAX CS-190® instrument. All dependent variables were analyzed in the continuous form, except for the RBC morphology. RBC count, WBC count, hemoglobin, hematocrit, platelet count, prothrombin time, and the RBC morphology also were analyzed in their discrete form, using Scripps Clinic normal ranges as cutpoints. RBC count, WBC count, hemoglobin, hematocrit, and platelet count were trichotomized as abnormal low, normal, and abnormal high.

RBC morphology was constructed from a number of laboratory conditions, many of which were minor abnormalities. Conditions considered to be abnormal for the 1997 follow-up included rouleaux, Burr cells, moderate microcytes, many microcytes, moderate macrocytes, moderate amount of ovalocytes, hypochromia, anisocytosis, slight polychromasia, slight baso-stippling, moderate stomatocytes, schistocytes, Howell-Jolly bodies, few teardrop cells, and Papperheimer bodies. Participants with few ovalocytes, few microcytes, few macrocytes, and slight macrocytes were considered to be normal for RBC morphology.

Participants testing positive for the human immunodeficiency virus (HIV) were excluded from the analysis of all variables. Participants with a fever (body temperature greater than or equal to 100° Fahrenheit) at the time of the examination were excluded from the analysis of all variables except prothrombin time. Participants taking an anticoagulant (such as Coumadin®) or aspirin at the time of the examination also were excluded from the analysis of prothrombin time. In addition, one participant had a hemolyzed specimen for prothrombin time and was excluded from the analysis of this variable.

15.1.3.2 Covariates

Age, race, military occupation, current level of cigarette smoking (cigarettes/day), and lifetime cigarette smoking history (pack-years) were used as covariates in adjusted statistical analyses evaluating the hematologic dependent variables.

Age, race, and military occupation were determined from military records. Current cigarette smoking and lifetime cigarette smoking history were based on questionnaire data. For lifetime cigarette smoking history, the respondent's average smoking was estimated over his lifetime based on his responses to the 1997 questionnaire, with 1 pack-year defined as 365 packs of cigarettes smoked during a single year.

15.1.4 Statistical Methods

Table 15-1 summarizes the statistical analyses performed for the hematologic assessment. The first part of this table describes the dependent variables analyzed. The second part of this table provides a further description of the covariates examined. A covariate was used in its continuous form whenever possible for all adjusted analyses; if necessary, if the covariate is inherently discrete (e.g., military occupations), or if a categorized form was needed to develop measures of association with the dependent variables, the

covariate was categorized as shown in Table 15-1. Table 15-2 provides a summary of the number of participants with missing dependent variable and covariate data. In addition, the number of participants excluded because of medical conditions is given.

Table 15-1. Statistical Analysis for the Hematologic Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Covariates ^a	Exclusions ^b	Statistical Analysis and Methods
RBC Count (million/mm ³)	LAB	D/C	Abnormal Low: <4.3 Normal: 4.3–5.9 Abnormal High: >5.9	(1)	(a)	U:PR,GLM A:PR,GLM
WBC Count (thousand/mm ³)	LAB	D/C	Abnormal Low: <4.5 Normal: 4.5–11.0 Abnormal High: >11.0	(1)	(a)	U:PR,GLM A:PR,GLM
Hemoglobin (gm/dl)	LAB	D/C	Abnormal Low: <13.9 Normal: 13.9–18.0 Abnormal High: >18.0	(1)	(a)	U:PR,GLM,CS A:PR,GLM
Hematocrit (percent)	LAB	D/C	Abnormal Low: <39.0 Normal: 39.0–55.0 Abnormal High: >55.0	(1)	(a)	U:PR,GLM,CS A:PR,GLM
Platelet Count (thousand/mm ³)	LAB	D/C	Abnormal Low: <130 Normal: 130–400 Abnormal High: >400	(1)	(a)	U:PR,GLM,CS A:PR,GLM L:PR,GLM
Prothrombin Time (seconds)	LAB	D/C	High: >12.3 Normal: ≤12.3	(1)	(b)	U:LR,GLM,CS A:LR,GLM
RBC Morphology	LAB	D	Abnormal Normal	(1)	(a)	U:LR A:LR
Absolute Neutrophils (segs) (thousand/mm ³)	LAB	C	--	(1)	(a)	U:GLM A:GLM
Absolute Neutrophils (bands) (thousand/mm ³)	LAB	D/C	Zero Nonzero	(1)	(a)	U:LR,GLM A:LR,GLM
Absolute Lymphocytes (thousand/mm ³)	LAB	C	--	(1)	(a)	U:GLM A:GLM
Absolute Monocytes (thousand/mm ³)	LAB	C	--	(1)	(a)	U:GLM A:GLM
Absolute Eosinophils (thousand/mm ³)	LAB	D/C	Zero Nonzero	(1)	(a)	U:LR,GLM A:LR,GLM
Absolute Basophils (thousand/mm ³)	LAB	D/C	Zero Nonzero	(1)	(a)	U:LR,GLM A:LR,GLM

^aCovariates:

(1): age, race, military occupation, current cigarette smoking, lifetime cigarette smoking history.

Table 15-1. Statistical Analysis for the Hematologic Assessment (Continued)

^bExclusions:

(a): participants with body temperatures greater than or equal to 100° Fahrenheit, participants testing positive for HIV.
 (b): participants testing positive for HIV, participants taking an anticoagulant (such as Coumadin®) or aspirin at the time of the examination.

Covariates

	Variable (Units)	Data Source	Data Form	Cutpoints
Age (years)		MIL	D/C	Born ≥1942 Born <1942
Race		MIL	D	Black Non-Black
Occupation		MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Current Cigarette Smoking (cigarettes/day)		Q-SR	D/C	0-Never 0-Former >0-20 >20
Lifetime Cigarette Smoking History (pack-years)		Q-SR	D/C	0 >0-10 >10

Abbreviations

Data Source:	LAB: 1997 laboratory results MIL: Air Force military records Q-SR: Health questionnaires (self-reported)
Data Form:	C: Continuous analysis only D: Discrete analysis only D/C: Discrete and continuous analyses for dependent variables; appropriate form for analysis (either discrete or continuous) for covariates
Statistical Analysis:	U: Unadjusted analysis A: Adjusted analysis L: Longitudinal analysis
Statistical Methods:	CS: Chi-square contingency table analysis (continuity-adjusted) GLM: General linear models analysis LR: Logistic regression analysis PR: Polytomous logistic regression analysis

Table 15-2. Number of Participants Excluded or with Missing Data for the Hematology Assessment

Variable	Variable Use	Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
		Ranch Hand	Comparison	Initial	1987	Ranch Hand	Comparison
Platelet Count	DEP	4	6	2	4	4	6
Prothrombin Time	DEP	0	1	0	0	0	1
Current Cigarette Smoking	COV	1	0	0	1	1	0
Lifetime Cigarette Smoking History	COV	2	1	1	2	2	1
Body Temperature $\geq 100^{\circ}$ Fahrenheit at the Time of the Physical Exam	EXC	1	0	1	1	1	0
HIV Positive	EXC	3	2	3	3	3	2
Taking an Anticoagulant or Aspirin at the Time of the Physical Exam	EXC	179	232	104	176	176	223

Note: DEP = Dependent variable.

COV = Covariate.

EXC = Exclusion.

870 Ranch Hands and 1,251 Comparisons.

482 Ranch Hands for initial dioxin; 863 Ranch Hands for 1987 dioxin.

863 Ranch Hands and 1,213 Comparisons for categorized dioxin.

Absolute neutrophils (bands), absolute eosinophils, and absolute basophils had a large number of measurements equal to 0 counts per mm^3 . The nonzero measurements exhibited a positively skewed distribution, and a logarithmic transformation, however, was applied to achieve an approximate normal distribution. The logarithmic transformation, however, could not be applied to the measurements equal to 0 counts per mm^3 . Consequently, these variables were analyzed in two forms: (a) a continuous analysis of the nonzero measurements and (b) a discrete analysis of the proportion of zero measurements.

15.1.4.1 Longitudinal Analysis

Longitudinal analyses on platelet count were conducted to evaluate the association of exposure to mean changes between the 1982 baseline examination and the 1997 follow-up examination.

15.2 RESULTS

15.2.1 Dependent Variable-Covariate Associations

Tests of associations were performed for each dependent variable in the hematology assessment with each covariate. Results are displayed in Appendix F, Table F-7. These associations are pairwise between the dependent variable and the covariate and are not adjusted for any other covariates. Participants who tested positive for HIV or who had a body temperature greater than or equal to 100° Fahrenheit were excluded from the analysis of all variables except prothrombin time. The analysis of prothrombin time included all participants except those testing positive for HIV or those taking an anticoagulant or aspirin at the time of the examination. In addition, one participant had a hemolyzed specimen for prothrombin time and was excluded from the analysis of this variable.

RBC count in its continuous form displayed a significant association with age ($p<0.001$), occupation ($p<0.001$), current cigarette smoking ($p=0.003$), and lifetime cigarette smoking history ($p=0.031$). RBC count decreased as age increased ($r=-0.181$). Among the occupational strata, enlisted groundcrew displayed the highest mean RBC count (5.01 million/mm³), followed by enlisted flyers (4.95 million/mm³), then officers (4.90 million/mm³). RBC count increased as current cigarette smoking increased ($r=0.064$). Conversely, as lifetime cigarette smoking increased, RBC count decreased ($r=-0.047$).

Tests of covariate associations involving RBC count in its discrete form revealed significant findings for age ($p=0.001$) and race ($p=0.001$). The prevalence of both low and high RBC abnormalities were higher among older participants and among Blacks.

Significant associations were found between WBC count in its continuous form and race ($p<0.001$), occupation ($p<0.001$), current cigarette smoking ($p<0.001$), and lifetime cigarette smoking history ($p<0.001$). Non-Blacks had a higher mean WBC count (6.71 thousand/mm³) than did Blacks (5.94 thousand/mm³). Enlisted groundcrew had the highest mean WBC count (6.91 thousand/mm³), followed by enlisted flyers (6.80 thousand/mm³), then officers (6.33 thousand/mm³). The current cigarette smoking and lifetime cigarette smoking history associations were positive ($r=0.395$ and $r=0.236$, respectively), indicating WBC count increased as the level of current cigarette smoking and the level of lifetime cigarette smoking history increased.

Analysis of WBC count in its discrete form revealed significant associations with race ($p=0.001$), current cigarette smoking ($p=0.001$), and lifetime cigarette smoking history ($p=0.001$), and a marginally significant association with occupation ($p=0.056$). Blacks displayed a higher percentage of abnormally low WBC counts (18.8%) than did non-Blacks (4.5%), but a lower percentage of abnormally high WBC counts (2.3%) than non-Blacks (3.7%). Officers displayed the highest percentage of abnormally low WBC counts (6.1%), but the lowest percentage of abnormally high WBC counts (2.3%). Enlisted flyers had the lowest percentage of abnormally low WBC counts (4.7%), while also displaying the highest percentage of abnormally high WBC counts (5.3%). Participants who had never smoked displayed the highest percentage of abnormally low WBC count levels (7.9%). The percentage of abnormally low WBC counts decreased as current cigarette smoking levels increased. The converse was true for the percentage of abnormally high WBC count levels. Participants smoking more than 20 cigarettes per day had the highest percentage of abnormally high WBC counts (16.1%), while nonsmokers had the lowest (1.4%). The tests of association with lifetime cigarette smoking history were similar to current cigarette smoking. Participants who had never smoked had the highest percentage of abnormally low WBC counts (7.9%), while participants in the more than 10 pack-years category displayed the highest percentage of abnormally high WBC counts (5.3%).

Tests of associations with hemoglobin in its continuous form revealed significant results for age ($p<0.001$), race ($p<0.001$), and current cigarette smoking ($p<0.001$). The association with occupation was marginally significant ($p=0.076$). Hemoglobin levels decreased as age increased ($r=-0.137$). Non-Blacks had a higher hemoglobin mean (15.36 gm/dl) than Blacks (14.77 gm/dl), while the highest hemoglobin mean was found among enlisted groundcrew (15.37 gm/dl). Hemoglobin levels increased as current cigarette smoking levels increased ($r=0.213$).

Hemoglobin in its discrete form also showed significant associations with age ($p=0.002$), race ($p=0.001$), and current cigarette smoking ($p=0.031$). The percentage of abnormally low hemoglobin levels was higher among older participants (8.3%) than among younger participants (4.5%). Blacks displayed a higher percentage of abnormally low hemoglobin levels (17.2%) than non-Blacks (6.0%). Former cigarette smokers had the highest percentage of abnormally low hemoglobin levels (8.1%), whereas 2.2 percent of participants smoking more than an average of 20 cigarettes per day had abnormally low

hemoglobin levels. Participants who smoked no more than 20 cigarettes per day displayed the highest percentage of abnormally high hemoglobin levels (1.1%), while participants who had never smoked had the lowest percentage (0.3%).

Significant associations with hematocrit in its continuous form were observed for age ($p<0.001$), race ($p<0.001$), occupation ($p=0.050$), and current cigarette smoking ($p<0.001$). A marginally significant association was found with lifetime cigarette smoking history ($p=0.085$). Hematocrit levels decreased as age increased ($r=-0.121$). The mean level of hematocrit was 45.65 percent for non-Blacks, compared to 44.49 percent for Blacks. Within the occupational strata, mean levels of hematocrit were 45.38 percent, 45.62 percent, and 45.74 percent for officers, enlisted flyers, and enlisted groundcrew, respectively. Hematocrit levels increased as current cigarette smoking increased ($r=0.209$). Hematocrit levels increased as lifetime cigarette smoking levels increased ($r=0.037$).

Age was significantly associated with hematocrit in its discrete form ($p=0.014$). The percentage of abnormally low hematocrit levels was higher among older participants (3.2%) than among younger participants (1.3%). The percentage of abnormally high levels of hematocrit was 0.3 percent for older participants compared to 0.2 percent for younger participants.

Platelet count in its continuous form displayed significant associations with age ($p<0.001$), occupation ($p=0.015$), current cigarette smoking ($p=0.005$), and lifetime cigarette smoking history ($p<0.001$). Tests of association revealed that platelet count decreased as age increased ($r=-0.120$). Platelet count means were highest among enlisted groundcrew (208.2 thousand/mm³), followed by enlisted flyers (205.5 thousand/mm³), then officers (201.6 thousand/mm³). Positive relations between platelet count and current cigarette smoking ($r=0.062$) and lifetime cigarette smoking history ($r=0.094$) indicated that platelet counts increased as the number of cigarettes per day and the number of pack-years increased, respectively.

Age was significantly associated with platelet count in its discrete form ($p=0.022$). Current cigarette smoking was marginally significantly associated with platelet count ($p=0.070$). The rate of abnormally low platelet counts was 3.7 percent among older participants and 1.9 percent among younger participants. The rate of abnormally high platelet counts was also higher among older participants (0.6%) than among younger participants (0.2%). Abnormally low platelet counts were most prevalent among participants who smoked no more than 20 cigarettes per day on average (3.4%). The highest percentage of abnormally high platelet counts was among participants smoking more than 20 cigarettes per day (2.2%).

Prothrombin time in its continuous form was significantly associated with age ($p<0.001$). Prothrombin time increased as age increased ($r=0.096$). The association was marginally significant between age and the discrete form of prothrombin time ($p=0.077$). A greater percentage of participants with abnormal (high) prothrombin times was observed in older participants (1.9%) than in younger participants (0.8%).

RBC morphology was significantly associated with age, race, current cigarette smoking, and lifetime cigarette smoking history ($p=0.013$, $p=0.001$, $p=0.001$, and $p=0.001$, respectively). The association between RBC morphology and occupation was marginally significant ($p=0.072$). Older participants and Blacks displayed the higher percentages of RBC morphology abnormalities (8.0% and 14.1%, respectively) as compared to younger participants and non-Blacks (5.2% and 6.3%, respectively). The RBC morphology abnormality rates increased as the levels of current cigarette smoking and lifetime cigarette smoking history each increased (3.7%, 7.3%, 9.7%, and 10.2% for the four current cigarette smoking categories and 3.7%, 7.0%, and 8.5% for the three lifetime cigarette smoking history categories). The percentages of abnormalities were 9.5 for enlisted flyers, 6.7 for enlisted groundcrew, and 5.8 for officers.

Examination of absolute neutrophils (segs) displayed significant covariate associations with race ($p<0.001$), occupation ($p<0.001$), current cigarette smoking ($p<0.001$), and lifetime cigarette smoking history ($p<0.001$). Mean absolute neutrophils (segs) levels were 3.88 thousand/mm³ for non-Blacks and 3.13 thousand/mm³ for Blacks. Within the occupational strata, mean absolute neutrophils (segs) levels were highest among enlisted groundcrew (4.00 thousand/mm³), followed by enlisted flyers (3.94 thousand/mm³), then officers (3.60 thousand/mm³). Absolute neutrophils (segs) increased as current cigarette smoking and lifetime cigarette smoking increased ($r=0.347$ and $r=0.214$, respectively).

For participants with positive absolute neutrophil (bands) levels, significant covariate associations were seen with age ($p=0.003$), race ($p<0.001$), current cigarette smoking ($p<0.001$), and lifetime cigarette smoking history ($p<0.001$). The level of absolute neutrophil (bands) increased as age, current cigarette smoking, and lifetime cigarette smoking history increased ($r=0.071$ for age, $r=0.188$, for current cigarette smoking; $r=0.133$ for lifetime cigarette smoking history). The significant absolute neutrophil (bands) association with race revealed a mean of 0.200 thousand/mm³ for non-Blacks and a mean of 0.120 thousand/mm³ for Blacks. A significant association with race also was revealed when the percentage of participants with measurements of zero absolute neutrophils (bands) was examined ($p=0.032$). For Blacks, 24.2 percent had zero absolute neutrophils, whereas 16.5 percent of non-Blacks had zero absolute neutrophils.

Absolute lymphocytes were significantly associated with age ($p<0.001$), race ($p=0.035$), occupation ($p<0.001$), current cigarette smoking ($p<0.001$), and lifetime cigarette smoking history ($p=0.002$). Absolute lymphocyte levels decreased as age increased ($r=-0.116$). Blacks displayed higher mean absolute lymphocyte levels (1.87 thousand/mm³) than did non-Blacks (1.75 thousand/mm³). Mean levels of absolute lymphocytes for each occupational stratum were 1.82 thousand/mm³ for enlisted groundcrew, 1.75 thousand/mm³ for enlisted flyers, and 1.68 thousand/mm³ for officers. Absolute lymphocyte levels increased as current cigarette smoking and lifetime cigarette smoking history increased ($r=0.195$ and $r=0.067$, respectively).

Results from the examination of covariate associations for absolute monocytes revealed significant associations with age ($p=0.043$), current cigarette smoking ($p<0.001$), and lifetime cigarette smoking history ($p<0.001$). Absolute monocyte levels increased as each of these covariates increased ($r=0.044$ for age, $r=0.160$ for current cigarette smoking, and $r=0.142$ for lifetime cigarette smoking history).

For participants with positive absolute eosinophil levels, significant associations were found between current cigarette smoking and lifetime cigarette smoking history ($p<0.001$ for each). Absolute eosinophils increased as current cigarette smoking and lifetime cigarette smoking history increased ($r=0.134$ and $r=0.086$, respectively). The percentage of participants with zero eosinophils was significantly associated with occupation ($p=0.005$). The percentages of participants with zero eosinophils were 14.7 for enlisted groundcrew, 11.5 for enlisted flyers, and 9.7 for officers.

Race, current cigarette smoking, and lifetime cigarette smoking history were significantly associated with basophils ($p=0.006$, $p<0.001$, and $p<0.001$, respectively) for participants whose absolute basophil level was positive. Mean levels of absolute basophils were 0.080 thousand/mm³ for non-Blacks, compared to 0.068 thousand/mm³ for Blacks. Basophils increased as current cigarette smoking and lifetime cigarette smoking history increased ($r=0.267$ and $r=0.168$, respectively). The proportion of participants with zero basophils was significantly associated with current cigarette smoking and lifetime cigarette smoking history ($p=0.033$ and $p=0.038$, respectively). Among levels of current cigarette smoking, the two highest percentages of participants with zero basophils were among participants who had never smoked (59.2%) and participants who were currently the heaviest smokers (59.9%). The percentage of participants with zero basophils decreased as the level of lifetime cigarette smoking history increased.

15.2.2 Exposure Analysis

The following section presents results of the statistical analyses of the dependent variables shown in Table 15-1. Dependent variables are derived from the laboratory portion of the 1997 follow-up examination.

Four models were examined for each dependent variable given in Table 15-1. The analyses of these models are presented below. Further details on dioxin and the modeling strategy are found in Chapters 2 and 7, respectively. These analyses were performed both unadjusted and adjusted for relevant covariates. Model 1 examined the relation between the dependent variable and group (i.e., Ranch Hand or Comparison). In this model, exposure was defined as "yes" for Ranch Hands and "no" for Comparisons without regard to the magnitude of the exposure. As an attempt to quantify exposure, three contrasts of Ranch Hands and Comparisons were performed along with the overall Ranch Hand versus Comparison contrast. These three contrasts compared Ranch Hands and Comparisons within each occupational category (i.e., officers, enlisted flyers, and enlisted groundcrew). As described in previous reports and Table 2-8, the average levels of exposure to dioxin were highest for enlisted groundcrew, followed by enlisted flyers, then officers.

Model 2 explored the relation between the dependent variable and an extrapolated initial dioxin measure for Ranch Hands who had a 1987 dioxin measurement greater than 10 parts per trillion (ppt). If a participant did not have a 1987 dioxin level, the 1992 level was used to estimate the initial dioxin level. If a participant did not have a 1987 or a 1992 dioxin level, the 1997 level was used to estimate the initial dioxin level. A statistical adjustment for the percentage of body fat at the time of the participant's blood measurement of dioxin is included in this model to account for body-fat-related differences in elimination rate (40).

Model 3 divided the Ranch Hands examined in Model 2 into two categories based on their initial dioxin measures. These two categories are referred to as "low Ranch Hand" and "high Ranch Hand." Two additional categories, Ranch Hands with 1987 serum dioxin levels at or below 10 ppt and Comparisons with 1987 serum dioxin levels at or below 10 ppt, were formed and included in the model. Ranch Hands with 1987 serum dioxin levels at or below 10 ppt are referred to as the "background Ranch Hand" category. Dioxin levels in 1992 were used if the 1987 level was not available, and dioxin levels in 1997 were used if the 1987 and 1992 levels were not available. These four categories—Comparisons, background Ranch Hands, low Ranch Hands, and high Ranch Hands—were used in Model 3 analyses. The relation between the dependent variable in each of the three Ranch Hand categories and the dependent variable in the "Comparison" category was examined. A fourth contrast, exploring the relation of the dependent variable in the combined low and high Ranch Hand categories relative to Comparisons, also was conducted. This combination is referred to in the tables as the "low plus high Ranch Hand" category. As in Model 2, a statistical adjustment for the percentage of body fat at the time of the participant's blood measurement of dioxin was included in this model.

Model 4 examined the relation between the dependent variable and 1987 lipid-adjusted dioxin levels in all Ranch Hands with a dioxin measurement. If a participant did not have a 1987 dioxin measurement, the 1992 measurement was used in determining the dioxin level. If a participant did not have a 1987 or a 1992 dioxin measurement, the 1997 measurement was used in determining the dioxin level.

15.2.2.1 Laboratory Examination Variables

15.2.2.1.1 RBC Count (Continuous)

The Model 3 unadjusted analysis of dioxin categories revealed a marginally significant difference between Ranch Hands in the low dioxin category and Comparisons. The mean RBC count was higher for Comparisons than for Ranch Hands in the low dioxin category (Table 15-3(e): $p=0.094$, difference of adjusted means = -0.05 million/mm³). Other analyses of dioxin categories in Model 3 and analyses from Models 1, 2, and 4 were all nonsignificant (Table 15-3(a-h): $p>0.10$ for all other analyses).

Table 15-3. Analysis of RBC Count (million/mm³) (Continuous)

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

Occupational Category	Group	n	Mean	Difference of Means (95% C.I.)	p-Value
<i>All</i>	<i>Ranch Hand</i>	866	4.95	-0.02 (-0.05,0.02)	0.318
	<i>Comparison</i>	1,249	4.96		
Officer	Ranch Hand	341	4.89	-0.03 (-0.09,0.02)	0.234
	Comparison	493	4.92		
Enlisted Flyer	Ranch Hand	151	4.92	-0.04 (-0.12,0.04)	0.333
	Comparison	187	4.97		
Enlisted Groundcrew	Ranch Hand	374	5.01	0.01 (-0.04,0.06)	0.753
	Comparison	569	5.00		

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

Occupational Category	Group	n	Adjusted Mean	Difference of Adj. Means (95% C.I.)	p-Value
<i>All</i>	<i>Ranch Hand</i>	864	4.95	-0.02 (-0.05,0.02)	0.311
	<i>Comparison</i>	1,248	4.96		
Officer	Ranch Hand	340	4.91	-0.03 (-0.08,0.02)	0.268
	Comparison	493	4.94		
Enlisted Flyer	Ranch Hand	151	4.94	-0.04 (-0.12,0.04)	0.343
	Comparison	187	4.98		
Enlisted Groundcrew	Ranch Hand	373	4.98	0.00 (-0.05,0.05)	0.919
	Comparison	568	4.97		

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

Initial Dioxin	Initial Dioxin Category Summary Statistics			Analysis Results for Log ₂ (Initial Dioxin)		
	n	Mean ^a	Adj. Mean ^a	R ²	Slope (Std. Error)	p-Value
Low	160	4.91	4.91	0.019	0.023 (0.014)	0.102
Medium	162	4.97	4.97			
High	156	4.99	4.99			

^a Adjusted for percent body fat at the time of the blood measurement of dioxin.

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

Table 15-3. Analysis of RBC Count (million/mm³) (Continuous) (Continued)

(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	R ²	Adj. Slope (Std. Error)	p-Value
Low	159	4.96		0.070	-0.004 (0.016)
Medium	162	4.98			
High	156	4.96			

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	Adj. Mean ^a	Difference of Adj. Mean vs. Comparisons (95% C.I.)	p-Value
Comparison	1,211	4.96	4.96		
Background RH	381	4.94	4.95	-0.01 (-0.06,0.03)	0.540
Low RH	239	4.92	4.92	-0.05 (-0.10,0.01)	0.094
High RH	239	4.99	4.98	0.02 (-0.04,0.07)	0.506
Low plus High RH	478	4.96	4.95	-0.01 (-0.05,0.03)	0.510

^a 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	Adj. Mean	Difference of Adj. Mean vs. Comparisons (95% C.I.)	p-Value
Comparison	1,210	4.97		
Background RH	380	4.97	0.00 (-0.04,0.05)	0.893
Low RH	238	4.93	-0.03 (-0.09,0.02)	0.230
High RH	239	4.94	-0.02 (-0.08,0.03)	0.441
Low plus High RH	477	4.94	-0.03 (-0.07,0.01)	0.196

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 15-3. Analysis of RBC Count (million/mm³) (Continuous) (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	Mean	R ²	Slope (Std. Error)	p-Value
Low	288	4.94	0.003	0.013 (0.009)	0.136
Medium	287	4.92			
High	284	4.99			

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	R ²	Adjusted Slope (Std. Error)	p-Value
Low	287	4.99	0.047	-0.001 (0.010)	0.941
Medium	286	4.96			
High	284	4.98			

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

15.2.2.1.2 RBC Count (Discrete)

All results from the analyses of RBC count in the discrete form were nonsignificant (Table 15-4(a-h); p>0.15 for each unadjusted and adjusted analysis of Models 1 through 4).

Table 15-4. Analysis of RBC Count (Discrete)**(a) MODEL 1: RANCH HANDS VS. COMPARISONS – UNADJUSTED**

Occupational Category	Group	n	Number (%)			Abnormal Low vs. Normal		Abnormal High vs. Normal	
			Abnormal Low	Normal	Abnormal High	Est. Relative Risk (95% C.I.)	p-Value	Est. Relative Risk (95% C.I.)	p-Value
<i>All</i>	<i>Ranch Hand</i>	866	42 (4.9)	818 (94.5)	6 (0.7)	<i>1.01 (0.67,1.51)</i>	<i>0.979</i>	<i>0.62 (0.24,1.61)</i>	<i>0.322</i>
	<i>Comparison</i>	1,249	60 (4.8)	1,175 (94.1)	14 (1.1)				
Officer	Ranch Hand	341	19 (5.6)	321 (94.1)	1 (0.3)	0.97 (0.53,1.77)	0.921	0.24 (0.03,1.98)	0.185
	Comparison	493	28 (5.7)	459 (93.1)	6 (1.2)				
Enlisted	Ranch Hand	151	11 (7.3)	138 (91.4)	2 (1.3)	2.03 (0.77,5.36)	0.155	1.29 (0.18,9.27)	0.800
	Flyer	187	7 (3.7)	178 (95.2)	2 (1.1)				
Enlisted	Ranch Hand	374	12 (3.2)	359 (96.0)	3 (0.8)	0.72 (0.36,1.45)	0.357	0.75 (0.19,3.02)	0.685
	Groundcrew	569	25 (4.4)	538 (94.6)	6 (1.1)				

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

Occupational Category	Abnormal Low vs. Normal			Abnormal High vs. Normal		
	Adj. Relative Risk (95% C.I.)		p-Value	Adj. Relative Risk (95% C.I.)		p-Value
<i>All</i>	<i>1.00 (0.66,1.51)</i>		<i>0.991</i>	<i>0.58 (0.22,1.54)</i>		<i>0.278</i>
Officer	0.95 (0.52,1.75)		0.869	0.23 (0.03,1.89)		0.170
Enlisted Flyer	1.97 (0.73,5.29)		0.180	1.25 (0.17,9.24)		0.830
Enlisted Groundcrew	0.75 (0.37,1.53)		0.426	0.73 (0.18,2.98)		0.660

Table 15-4. Analysis of RBC Count (Discrete) (Continued)

(c) MODEL 2: RANCH HANDS — INITIAL DIOXIN — UNADJUSTED					
Initial Dioxin Category Summary Statistics				Analysis Results for \log_2 (Initial Dioxin) ^a	
Initial Dioxin Category	n	Number (%)		Abnormal Low vs. Normal	Abnormal High vs. Normal
		Abnormal Low	Normal	Abnormal High	Est. Relative Risk (95% C.I.) ^b p-Value
Low	160	9 (5.6)	150 (93.8)	1 (0.6)	0.79 (0.53,1.15) 0.220
Medium	162	7 (4.3)	151 (93.2)	4 (2.5)	
High	156	5 (3.2)	151 (96.8)	0 (0.0)	

^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)				Abnormal High vs. Normal	
n	Abnormal Low vs. Normal		p-Value	Abnormal High vs. Normal	
	Adj. Relative Risk (95% C.I.) ^a			Adj. Relative Risk (95% C.I.) ^a	p-Value
477	0.95 (0.64, 1.41)		0.804	0.88 (0.39, 1.99)	0.751

^a Relative risk for a twofold increase in initial dioxin.

Note: Results are not adjusted for race because of the sparse number of participants with an abnormal high RBC count.

Table 15-4. Analysis of RBC Count (Discrete) (Continued)

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY — UNADJUSTED								
Dioxin Category	n	Number (%)			Abnormal Low vs. Normal		Abnormal High vs. Normal	
		Abnormal Low	Normal	Abnormal High	Est. Relative Risk (95% C.I.)^{ab}	p-Value	Est. Relative Risk (95% C.I.)^{ab}	p-Value
Comparison	1,211	55 (4.5)	1,142 (94.3)	14 (1.2)				
Background RH	381	19 (5.0)	361 (94.8)	1 (0.3)	1.09 (0.64,1.87)	0.757	0.26 (0.03,1.99)	0.195
Low RH	239	12 (5.0)	225 (94.1)	2 (0.8)	1.11 (0.58,2.10)	0.753	0.69 (0.15,3.06)	0.623
High RH	239	9 (3.8)	227 (95.0)	3 (1.3)	0.83 (0.40,1.70)	0.603	0.94 (0.26,3.33)	0.921
Low plus High RH	478	21 (4.4)	452 (94.6)	5 (1.1)	0.96 (0.57,1.61)	0.868	0.80 (0.28,2.30)	0.683

^aRelative risk and confidence interval relative to Comparisons.^bAdjusted for percent body fat at the time of the blood measurement of dioxin.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin \leq 10 ppt.Background (Ranch Hand): 1987 Dioxin \leq 10 ppt.Low (Ranch Hand): 1987 Dioxin $>$ 10 ppt, 10 ppt $<$ Initial Dioxin \leq 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	Abnormal Low vs. Normal			Abnormal High vs. Normal			
		Adj. Relative Risk (95% C.I.)^a	p-Value	Adj. Relative Risk (95% C.I.)^a	p-Value			
Comparison	1,210							
Background RH	380	1.07 (0.61,1.86)	0.818	0.25 (0.03,1.99)	0.192			
Low RH	238	0.92 (0.48,1.78)	0.809	0.54 (0.12,2.48)	0.431			
High RH	239	1.04 (0.49,2.23)	0.917	1.16 (0.31,4.42)	0.827			
Low plus High RH	477	0.98 (0.57,1.68)	0.942	0.79 (0.27,2.33)	0.676			

^aRelative risk and confidence interval relative to Comparisons.

Note: RH = Ranch Hand.

Comparison: 1987 Dioxin \leq 10 ppt.Background (Ranch Hand): 1987 Dioxin \leq 10 ppt.Low (Ranch Hand): 1987 Dioxin $>$ 10 ppt, 10 ppt $<$ Initial Dioxin \leq 94 ppt.High (Ranch Hand): 1987 Dioxin $>$ 10 ppt, Initial Dioxin $>$ 94 ppt.

Table 15-4. Analysis of RBC Count (Discrete) (Continued)**(g) MODEL 4: RANCH HANDS — 1987 DIOXIN — UNADJUSTED**

1987 Dioxin Category	n	1987 Dioxin Category Summary Statistics		Analysis Results for $\log_2(1987 \text{ Dioxin} + 1)$					
		Abnormal Low	Number (%)	Abnormal High	Est. Relative Risk (95% C.I.) ^a	p-Value	Abnormal High vs. Normal	Est. Relative Risk (95% C.I.) ^a	p-Value
Low	288	13 (4.5)	274 (95.1)	1 (0.4)	0.91 (0.73,1.14)	0.405	1.16 (0.69,1.95)	0.566	
Medium	287	16 (5.6)	270 (94.1)	1 (0.4)					
High	284	11 (3.9)	269 (94.7)	4 (1.4)					

^aRelative 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

n	Analysis Results for $\log_2(1987 \text{ Dioxin} + 1)$			
	Abnormal Low vs. Normal	Abnormal High vs. Normal		
857	Adj. Relative Risk (95% C.I.) ^a 0.91 (0.69,1.21)	Adj. Relative Risk (95% C.I.) ^a 1.10 (0.60,2.00)	p-Value 0.511	p-Value 0.764

^aRelative risk for a twofold increase in 1987 dioxin.

15.2.2.1.3 WBC Count (Continuous)

Each Model 1 contrast examining WBC count differences between Ranch Hands and Comparison means was nonsignificant, with and without covariate adjustment (Table 15-5(a,b): $p>0.35$ for each contrast).

Table 15-5. Analysis of WBC Count (thousand/mm³) (Continuous)

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

Occupational Category	Group	n	Mean ^a	Difference of Means (95% C.I.) ^b	p-Value ^c
<i>All</i>	<i>Ranch Hand</i>	866	6.67	0.02 --	0.789
	<i>Comparison</i>	1,249	6.65		
Officer	Ranch Hand	341	6.33	0.00 --	0.970
	Comparison	493	6.33		
Enlisted Flyer	Ranch Hand	151	6.72	-0.14 --	0.474
	Comparison	187	6.86		
Enlisted Groundcrew	Ranch Hand	374	6.97	0.11 --	0.358
	Comparison	569	6.86		

^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
<i>All</i>	<i>Ranch Hand</i>	864	6.26	0.00 --	0.974
	<i>Comparison</i>	1,248	6.26		
Officer	Ranch Hand	340	6.03	0.00 --	0.972
	Comparison	493	6.03		
Enlisted Flyer	Ranch Hand	151	6.17	-0.14 --	0.377
	Comparison	187	6.31		
Enlisted Groundcrew	Ranch Hand	373	6.55	0.05 --	0.648
	Comparison	568	6.50		

^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 15-5. Analysis of WBC Count (thousand/mm³) (Continuous) (Continued)

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

Initial Dioxin	Initial Dioxin Category Summary Statistics			Analysis Results for Log ₂ (Initial Dioxin) ^b		
	n	Mean ^a	Adj. Mean ^{ab}	R ²	Slope (Std. Error) ^c	p-Value
Low	160	6.48	6.50	0.022	0.019 (0.009)	0.035
Medium	162	6.91	6.92			
High	156	6.90	6.88			

^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 WBC count versus log₂ (initial dioxin).

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

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

Initial Dioxin	Initial Dioxin Category Summary Statistics		Analysis Results for Log ₂ (Initial Dioxin)		
	n	Adj. Mean ^a	R ²	Adj. Slope (Std. Error) ^b	p-Value
Low	159	6.08	0.213	0.008 (0.009)	0.414
Medium	162	6.29			
High	156	6.22			

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of WBC count versus log₂ (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	6.64	6.64		
Background RH	381	6.53	6.57	-0.07 --	0.493
Low RH	239	6.57	6.56	-0.08 --	0.491
High RH	239	6.96	6.92	0.28 --	0.029
Low plus High RH	478	6.76	6.73	0.09 --	0.324

^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 15-5. Analysis of WBC Count (thousand/mm³) (Continuous) (Continued)

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED		Difference of Adj. Mean vs. Comparisons (95% C.I.) ^b			p-Value ^c
Dioxin Category	n	Adj. Mean ^a			
Comparison	1,210	6.27			
Background RH	380	6.28	0.01 --		0.902
Low RH	238	6.18	-0.09 --		0.383
High RH	239	6.33	0.06 --		0.600
Low plus High RH	477	6.26	-0.01 --		0.831

^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 \leq 10 ppt.

Background (Ranch Hand): 1987 Dioxin \leq 10 ppt.

Low (Ranch Hand): 1987 Dioxin $>$ 10 ppt, 10 ppt $<$ Initial Dioxin \leq 94 ppt.

High (Ranch Hand): 1987 Dioxin $>$ 10 ppt, Initial Dioxin $>$ 94 ppt.

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED			Analysis Results for Log ₂ (1987 Dioxin + 1) ^b		
1987 Dioxin Category Summary Statistics			R ²	Slope (Std. Error) ^b	p-Value
1987 Dioxin	n	Mean ^a			
Low	288	6.45	0.007	0.015 (0.006)	0.013
Medium	287	6.60			
High	284	6.95			

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of WBC count versus log₂ (1987 dioxin + 1).

Note: Low = \leq 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)		
1987 Dioxin Category Summary Statistics			R ²	Adjusted Slope (Std. Error) ^b	p-Value
1987 Dioxin	n	Adj. Mean ^a			
Low	287	6.09	0.219	0.007 (0.006)	0.263
Medium	286	6.18			
High	284	6.32			

^a Transformed from natural logarithm scale.

^b Slope and standard error based on natural logarithm of WBC count versus log₂ (1987 dioxin + 1).

Note: Low = \leq 7.9 ppt; Medium = $>$ 7.9–19.6 ppt; High = $>$ 19.6 ppt.