Table 9-15. Longitudinal Analysis of Erythrocyte Sedimentation Rate (mm/hr) (Continuous)

(a) MODEL 1: RANCH HANDS VS. COMPARISONS

Occupational Category	Group	Mean[a]/(n) Examination 1982	1985	1987	1992	1997	Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
All	*Ranch Hand*	*1.83*	*481*	*5.06*	*8.03*	*4.87*	*3.05*	*0.04*	*0.813*
		(819)	*(801)*	*(792)*	*(797)*	*(819)*			
	Comparison	*1.59*	*4.67*	*4.86*	*7.57*	*4.59*	*3.01*		
		(976)	*(958)*	*(949)*	*(956)*	*(976)*			
Officer	Ranch Hand	1.83	4.71	4.81	7.39	4.44	2.61	–0.34	0.213
		(312)	(308)	(304)	(307)	(312)			
	Comparison	1.44	4.65	4.72	7.39	4.38	2.95		
		(380)	(374)	(368)	(375)	(380)			
Enlisted Flyer	Ranch Hand	2.13	5.30	6.04	8.94	5.38	3.25	0.08	0.878
		(148)	(145)	(143)	(145)	(148)			
	Comparison	2.11	5.02	5.02	8.44	5.28	3.17		
		(145)	(144)	(143)	(143)	(145)			
Enlisted Groundcrew	Ranch Hand	1.71	4.71	4.92	8.25	5.07	3.36	0.37	0.138
		(359)	(348)	(345)	(345)	(359)			
	Comparison	1.58	4.58	4.93	7.46	4.57	2.99		
		(451)	(440)	(438)	(438)	(451)			

[a] Transformed from natural logarithm scale of erythrocyte sedimentation rate + 0.1.
[b] Difference between 1997 and 1982 examination means after transformation to original scale.
[c] P-value is based on analysis of natural logarithm of erythrocyte sedimentation rate + 0.1; results adjusted for natural logarithm of erythrocyte sedimentation rate + 0.1 in 1982 and age in 1997.

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

Table 9-15. Longitudinal Analysis of Erythrocyte Sedimentation Rate (mm/hr) (Continuous) (Continued)

(b) MODEL 2: RANCH HANDS – INITIAL DIOXIN							
Initial Dioxin Category Summary Statistics						Analysis Results for Log_2 (Initial Dioxin)[b]	
	Mean[a]/(n) Examination						
Initial Dioxin	1982	1985	1987	1992	1997	Adjusted Slope (Std. Error)	p-Value
Low	1.71 (154)	4.82 (151)	4.99 (153)	7.94 (149)	4.74 (154)	0.045 (0.031)	0.146
Medium	2.25 (159)	5.52 (156)	5.71 (156)	9.62 (156)	5.94 (159)		
High	1.76 (153)	4.94 (150)	5.53 (148)	8.42 (150)	5.10 (153)		

[a] Transformed from natural logarithm scale of erythrocyte sedimentation rate + 0.1.

[b] Results based on difference between natural logarithm of 1997 erythrocyte sedimentation rate + 0.1 and natural logarithm of 1982 erythrocyte sedimentation rate + 0.1 versus $\log_2$ (initial dioxin); results adjusted for percent body fat at the date of the blood measurement of dioxin, natural logarithm of 1982 erythrocyte sedimentation rate + 0.1, and age in 1997.

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

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

Table 9-15. Longitudinal Analysis of Erythrocyte Sedimentation Rate (mm/hr) (Continuous) (Continued)

(c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY								
Dioxin Category	Mean[a]/(n) Examination					Exam. Mean Change[b]	Difference of Exam. Mean Change	p-Value[c]
	1982	1985	1987	1992	1997			
Comparison	1.60 (948)	4.66 (933)	4.85 (923)	7.55 (929)	4.60 (948)	3.00		
Background RH	1.72 (347)	4.45 (339)	4.63 (330)	7.27 (337)	4.39 (347)	2.67	–0.33	0.220
Low RH	1.92 (230)	5.06 (224)	5.24 (227)	8.59 (223)	5.12 (230)	3.20	0.20	0.784
High RH	1.87 (236)	5.11 (233)	5.56 (230)	8.70 (232)	5.37 (236)	3.50	0.50	0.050
Low plus High RH	1.89 (466)	5.09 (457)	5.40 (457)	8.65 (455)	5.25 (466)	3.35	0.35	0.143

[a] Transformed from natural logarithm scale of erythrocyte sedimentation rate + 0.1.
[b] Difference between 1997 and 1982 examination means after transformation to original scale.
[c] P-value is based on analysis of natural logarithm of 1997 erythrocyte sedimentation rate + 0.1; results adjusted for percent body fat at the date of the blood measurement of dioxin, natural logarithm of 1982 erythrocyte sedimentation rate + 0.1, and age in 1997.

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.

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

9.2.3.3.2 Erythrocyte Sedimentation Rate (Discrete)

Longitudinal analyses of erythrocyte sedimentation rate in its discrete form were conducted to examine the relation between abnormal erythrocyte sedimentation rates and group, initial dioxin, and categorized dioxin for participants at the 1997 follow-up. Only participants with normal erythrocyte sedimentation rates in 1982 were included in the study.

Analyses were statistically significant when erythrocyte sedimentation rate differences were examined across all occupations (Table 9-16(a): Adj. RR=1.66, p=0.016). The results revealed that the percentage of abnormal erythrocyte sedimentation rates for Ranch Hands was higher than for Comparisons (7.0% and 4.4%, respectively). Erythrocyte sedimentation rates compared within the officer strata did not significantly differ (p=0.847). Within the enlisted flyer stratum, the Ranch Hands versus Comparison contrast was marginally significant (Adj. RR=2.61, p=0.077). More Ranch Hand (9.0%) than

Comparison (3.7%) enlisted flyers had abnormal erythrocyte sedimentation rates. In addition, results were significant (Adj. RR=2.03, p=0.025) for the enlisted groundcrew stratum. Percentages of abnormal erythrocyte sedimentation rates were 7.7 for Ranch Hand and 4.2 for Comparison enlisted groundcrew.

A significant positive association between initial dioxin and erythrocyte sedimentation rate was found (Table 9-16(b): Adj. RR=1.36, p=0.022). The analyses indicated that erythrocyte sedimentation rate increased as initial dioxin level increased.

Analyses of associations between erythrocyte sedimentation rates and categorized dioxin revealed significant differences between Comparisons and Ranch Hands in the high and Ranch Hands in the low and high dioxin categories combined (Table 9-16(c): Adj. RR=2.38, p=0.003 and Adj. RR=1.88, p=0.010, respectively). Both contrasts indicate that more Ranch Hands than Comparison had a higher percentage of abnormal erythrocyte sedimentation rates (8.7% for Ranch Hands in the high dioxin category, 7.7% for Ranch Hands in the low and high dioxin categories combined, and 4.3% for Comparisons). The contrasts involving the background and low Ranch Hand dioxin categories were both nonsignificant (p>0.22 for each contrast).

Table 9-16. Longitudinal Analysis of Erythrocyte Sedimentation Rate (Discrete)

(a) MODEL 1: RANCH HANDS VS. COMPARISONS

Occupational Category	Group	Number (%) Abnormal/(n) Examination				
		1982	1985	1987	1992	1997
All	***Ranch Hand***	***19 (2.3)*** ***(819)***	***50 (6.2)*** ***(801)***	***54 (6.8)*** ***(792)***	***130 (16.3)*** ***(797)***	***67 (8.2)*** ***(819)***
	Comparison	***39 (4.0)*** ***(976)***	***50 (5.2)*** ***(958)***	***45 (4.7)*** ***(949)***	***153 (16.0)*** ***(956)***	***57 (5.8)*** ***(976)***
Officer	Ranch Hand	6 (1.9) (312)	10 (3.3) (308)	12 (4.0) (304)	38 (12.4) (307)	18 (5.8) (312)
	Comparison	12 (3.2) (380)	15 (4.0) (374)	14 (3.8) (368)	49 (13.1) (375)	26 (6.8) (380)
Enlisted Flyer	Ranch Hand	4 (2.7) (148)	13 (9.0) (145)	15 (10.5) (143)	30 (20.7) (145)	16 (10.8) (148)
	Comparison	9 (6.2) (145)	10 (6.9) (144)	5 (3.5) (143)	27 (18.9) (143)	5 (3.5) (145)
Enlisted Groundcrew	Ranch Hand	9 (2.5) (359)	27 (7.8) (348)	27 (7.8) (345)	62 (18.0) (345)	33 (9.2) (359)
	Comparison	18 (4.0) (451)	25 (5.7) (440)	26 (5.9) (438)	77 (17.6) (438)	26 (5.8) (451)

Table 9-16. Longitudinal Analysis of Erythrocyte Sedimentation Rate (Discrete) (Continued)

Occupational Category	Group	Normal in 1982: n in 1997	Normal in 1982: Number (%) Abnormal in 1997	Adj. Relative Risk (95% C.I.)[a]	p-Value[a]
All	***Ranch Hand***	***800***	***56 (7.0)***	***1.66 (1.09,2.52)***	***0.016***
	Comparison	***937***	***41 (4.4)***		
Officer	Ranch Hand	306	16 (5.2)	1.07 (0.53,2.14)	0.847
	Comparison	368	18 (4.9)		
Enlisted Flyer	Ranch Hand	144	13 (9.0)	2.61 (0.90,7.55)	0.077
	Comparison	136	5 (3.7)		
Enlisted Groundcrew	Ranch Hand	350	27 (7.7)	2.03 (1.09,3.77)	0.025
	Comparison	433	18 (4.2)		

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

Note: Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations. Statistical analyses are based only on participants who had a normal erythrocyte sedimentation rate (≤12 mm/hr) in 1982 (see Chapter 7, Statistical Methods).

(b) MODEL 2: RANCH HANDS — INITIAL DIOXIN

Initial Dioxin	Number (%) Abnormal/(n) Examination: 1982	1985	1987	1992	1997
Low	5 (3.3) (154)	13 (8.6) (151)	7 (4.6) (153)	27 (18.1) (149)	11 (7.1) (154)
Medium	3 (1.9) (159)	14 (9.0) (156)	16 (10.3) (156)	33 (21.2) (156)	18 (11.3) (159)
High	4 (2.6) (153)	13 (8.7) (150)	14 (9.5) (148)	26 (17.3) (150)	15 (9.8) (153)

Table 9-16. Longitudinal Analysis of Erythrocyte Sedimentation Rate (Discrete) (Continued)

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
	Normal in 1982			
Initial Dioxin	n in 1997	Number (%) Abnormal in 1997	Adj. Relative Risk (95% C.I.)[b]	p-Value
Low	149	8 (5.4)	1.36 (1.05,1.76)	0.022
Medium	156	15 (9.6)		
High	149	12 (8.1)		

[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 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations. Statistical analyses are based only on participants who had a normal erythrocyte sedimentation rate (≤ 12 mm/hr) in 1982 (see Chapter 7, Statistical Methods).

(c) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY					
	Number (%) Abnormal/(n) Examination				
Dioxin Category	1982	1985	1987	1992	1997
Comparison	39 (4.1) (948)	50 (5.4) (933)	42 (4.6) (923)	148 (15.9) (929)	55 (5.8) (948)
Background RH	7 (2.0) (347)	10 (3.0) (339)	17 (5.2) (330)	42 (12.5) (337)	22 (6.3) (347)
Low RH	7 (3.0) (230)	19 (8.5) (224)	14 (6.2) (227)	43 (19.3) (223)	20 (8.7) (230)
High RH	5 (2.1) (236)	21 (9.0) (233)	23 (10.0) (230)	43 (18.5) (232)	24 (10.2) (236)
Low plus High RH	12 (2.6) (466)	40 (8.8) (457)	37 (8.1) (457)	86 (18.9) (455)	44 (9.4) (466)

Table 9-16. Longitudinal Analysis of Erythrocyte Sedimentation Rate (Discrete) (Continued)

Dioxin Category	Normal in 1982: n in 1997	Normal in 1982: Number (%) Abnormal in 1997	Adj. Relative Risk (95% C.I.)[ab]	p-Value[b]
Comparison	909	39 (4.3)		
Background RH	340	20 (5.9)	1.40 (0.80,2.45)	0.238
Low RH	223	15 (6.7)	1.47 (0.79,2.73)	0.225
High RH	231	20 (8.7)	2.38 (1.34,4.23)	0.003
Low plus High RH	454	35 (7.7)	1.88 (1.16,3.03)	0.010

[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 ≤ 10 ppt.
Background (Ranch Hand): 1987 Dioxin ≤ 10 ppt.
Low (Ranch Hand): 1987 Dioxin >10 ppt, 10 ppt < Initial Dioxin ≤ 94 ppt.
High (Ranch Hand): 1987 Dioxin >10 ppt, Initial Dioxin > 94 ppt.

Summary statistics for 1985 are provided for reference purposes for participants who attended the 1982, 1985, and 1997 examinations. Summary statistics for 1987 are provided for reference purposes for participants who attended the 1982, 1987, and 1997 examinations. Summary statistics for 1992 are provided for reference purposes for participants who attended the 1982, 1992, and 1997 examinations. Statistical analyses are based only on participants who had a normal erythrocyte sedimentation rate (≤ 12 mm/hr) in 1982 (see Chapter 7, Statistical Methods).

9.3 DISCUSSION

In clinical medicine, the assessment of an individual's general state of health is based on subjective and objective indices including the individual's history, physical examination, and laboratory testing. The variables analyzed in this chapter are frequently employed by clinicians in outpatient practice and were selected to be sensitive to the overall state of health rather than specific to any organ system.

The clinical evaluation of the patient begins with the medical history, which often begins with an intentionally open inquiry into the patient's self-perception of health. In the current examinations, as in most of the previous, a significantly higher percentage of Ranch Hand participants than Comparisons perceived themselves to be in poor health (14.3 percent versus 10.4 percent). Once again the contrast was most apparent in enlisted groundcrew, who had the highest average level of dioxin exposure (18.0 percent of Ranch Hands versus 12.8 percent of Comparisons). In a dose-response pattern, an increasing body burden of dioxin was significantly associated (p=0.002) with negative self-perceptions of health in Ranch Hands in the low, medium, and high 1987 dioxin categories (8.0 percent, 14.3 percent, and 19.3 percent, respectively); this association became marginally significant (p=0.079) with adjustment for relevant covariates. No group differences were noted in the appearance of illness or relative age, as recorded by examining physicians, nor were these variables correlated with serum dioxin levels in the Ranch Hand cohort.

The body fat measure is an easily derived index and, to the extent that it can reflect significant weight gain or loss over time, it can serve as a valuable clinical clue to the presence of occult disease. The prevalence of obesity (>25 percent body fat) was similar in the Ranch Hand and Comparison cohorts. In Ranch Hands by both continuous and discrete analyses, a consistent and highly significant (p<0.001 for both) positive association was noted between obesity and the 1987 serum dioxin level. Although a mobile equilibrium exists between serum dioxin and adipose tissue, the current results confirm those of the 1992 examinations and suggest a difference in dioxin pharmacokinetics in obese versus lean individuals.

The erythrocyte sedimentation rate can be a sensitive, if nonspecific, index of general health. The effect of age on the erythrocyte sedimentation rate is pertinent to the longitudinal design of the current study: a rate as high as 40 millimeters per hour is not considered unusual at age 65. Extreme elevations in the erythrocyte sedimentation rate consistently are associated with serious underlying infections, inflammation, or malignant disease processes.

In prior examinations, erythrocyte sedimentation rate analyses have yielded inconsistent results. In the 1985 and 1987 examinations (but not in 1982 or 1992), abnormally elevated erythrocyte sedimentation rates were significantly more prevalent in Ranch Hands than Comparisons. In the 1987 and 1992 examinations, dioxin analyses raised the possibility of a subtle dose-response inflammatory effect occurring in association with initial and then current serum dioxin levels. In the 1992 examinations, for example, the Ranch Hand enlisted groundcrew, the occupation with the highest average dioxin level, had a slightly higher mean erythrocyte sedimentation rate than Comparisons, but the difference (9.27 mm/hr versus 8.43 mm/hr) cannot be considered clinically meaningful. In the models that employed 1987 serum dioxin levels, the analyses yielded results that were consistent with a subtle dose-response effect, but the differences were slight and of uncertain biologic meaning.

Similarly, in this current study, by both continuous and discrete analyses, significant associations were noted between the erythrocyte sedimentation rate and 1987 serum dioxin levels. In a pattern consistent with a dose-response effect, Ranch Hand participants in the low, medium, and high 1987 dioxin categories had abnormally elevated erythrocyte sedimentation rates of 6.6, 8.0, and 9.7 percent, respectively. By continuous analysis, the differences in the means were so slight (adjusted means of 4.34 mm/hr, 4.62 mm/hr, and 5.29 mm/hr in the low, medium, and high 1987 dioxin categories, respectively) as to be of doubtful clinical meaning. As in the 1992 examinations, the erythrocyte sedimentation rate analyses found no group differences between the Ranch Hand and Comparison cohorts.

Dependent variable-covariate analyses confirm numerous associations that have been documented in previous AFHS examinations and that are well-established in clinical practice. Consequent to the higher incidence of nicotine-related cardiovascular and pulmonary disease that occurs by middle age, cigarette smokers often appear older and more chronically ill than nonsmokers and perceive themselves as such. That the highest prevalence of obesity (33.6 percent) was found in reformed smokers is consistent with the weight gain that so often occurs with smoking cessation. Given the high incidence of chronic bronchitis associated with cigarette use, it is not surprising that the highest prevalence of abnormally elevated erythrocyte sedimentation rates (12.4 percent) was noted in those smoking more than one pack per day.

Analyses based on associations with occupation confirm previous AFHS results. As a group, officers continue to appear healthier than enlisted personnel by several indices including perceptions of health, relative age appearance, and body fat. Older participants were more likely to have abnormally elevated erythrocyte sedimentation rates than younger participants.

Longitudinal analyses confirm results and trends that have been established over 15 years of observation. At the baseline examination in 1982, the prevalence of self-perceived ill health was significantly greater in Ranch Hands than Comparisons (18.7 percent versus 13.2 percent). By 1987, despite advancing age, the percentage of Ranch Hands and Comparisons reporting ill health declined to 5.5 percent and 4.4 percent, respectively. In 1992 this trend was reversed, particularly in those Ranch Hands in the medium and high categories of current and initial levels of serum dioxin. In the 1997 examinations there has been a close to identical increase (40 percent) in the prevalence of reported poor health in each cohort (14.4 percent versus 10.6 percent), a trend that is consistent with the increased incidence of chronic illness in any aging population and that is now independent of all indices of exposure to dioxin. In contrast, in neither the appearance of illness or distress nor in relative age appearance were there any significant associations with the 1987 body burden of dioxin.

In the 1985 and 1987 examinations, Ranch Hand participants were noted to have a higher percentage of abnormal erythrocyte sedimentation rates than Comparisons and, in 1987, a significant positive association was found between group and the change in the percentage of abnormal erythrocyte sedimentation rates. In 1992, the prevalence of abnormal erythrocyte sedimentation rates was close to identical in the two cohorts with no evidence of a dioxin effect. In the current study, Ranch Hands once again have a significantly higher percentage of abnormal erythrocyte sedimentation rates than Comparisons (7.0 percent versus 4.4 percent of participants considered normal in 1982) in a pattern consistent with a dose response. This pattern also was present with categorized dioxin, where 8.7 percent of Ranch Hands with the highest levels of serum dioxin had an abnormally elevated erythrocyte sedimentation rate, compared with 4.3 percent of Comparisons ($p=0.003$). This positive association raises the possibility of a subtle inflammatory, infectious, or occult malignant disease process related to the body burden of dioxin.

In summary, consistent with all previous examinations, Ranch Hands continue to perceive themselves as less healthy than Comparisons. Since the last examinations in 1992, a comparable and significant increase in the prevalence of self-perceived ill health has occurred in both cohorts and is consistent with the inevitable development of chronic disease in any aging population.

9.4 SUMMARY

9.4.1 Model 1: Group Analysis

The unadjusted and adjusted group analyses (Ranch Hands versus Comparisons) produced similar results for each variable examined within the general health assessment. The self-perception of health analysis revealed significant differences among Ranch Hands and Comparisons across all occupations and within the enlisted groundcrew stratum. For both contrasts, more Ranch Hands than Comparisons indicated their health as fair or poor. All other group analyses were nonsignificant. The results are summarized in Table 9-17.

Longitudinal analyses of erythrocyte sedimentation rate in its discrete form indicated that significantly more Ranch Hands then Comparisons were normal in 1982 and abnormal in 1997. This difference was noted in the two enlisted strata.

Table 9-17. Summary of Group Analysis (Model 1) for General Health Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED All	Officer	Enlisted Flyer	Enlisted Groundcrew
Questionnaire				
Self-perception of Health (D)	+0.007	NS	NS	+0.028
Physical Examination				
Appearance of Illness or Distress (D)	NS	NS	NS	NS
Relative Age Appearance (D)	NS	NS	NS	NS
Body Fat (C)	ns	ns	ns	ns
Body Fat (D)	ns	NS	ns	ns
Laboratory				
Erythrocyte Sedimentation Rate (C)	NS	ns	ns	NS
Erythrocyte Sedimentation Rate (D)	NS	ns	NS	NS

Note: NS or ns: Not significant (p>0.10).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥ 1.00.

P-value given if p≤0.05.

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

Variable	ADJUSTED All	Officer	Enlisted Flyer	Enlisted Groundcrew
Questionnaire				
Self-perception of Health (D)	+0.010	NS	NS	+0.035
Physical Examination				
Appearance of Illness or Distress (D)	NS	NS	NS	NS
Relative Age Appearance (D)	NS	NS	NS	NS
Body Fat (C)	ns	ns	ns	ns
Body Fat (D)	ns	NS	ns	ns
Laboratory				
Erythrocyte Sedimentation Rate (C)	NS	ns	ns	NS
Erythrocyte Sedimentation Rate (D)	NS	ns	NS	NS

Note: NS or ns: Not significant (p>0.10).
C: Continuous analysis.
D: Discrete analysis.
+: Relative risk ≥ 1.00.

P-value given if p≤0.05.

Table 9-17. Summary of Group Analysis (Model 1) for General Health Variables (Ranch Hands vs. Comparisons) (Continued)

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

9.4.2 Model 2: Initial Dioxin Analysis

The unadjusted analysis of body fat in its continuous form revealed a marginally significant association between body fat and initial dioxin. The relative risk estimate for the adjusted analysis became significant, with body fat increasing as initial dioxin increased. All remaining analyses of other variables examined revealed nonsignificant results, as shown in Table 9-18.

A significant relation was observed in longitudinal analyses between abnormal erythrocyte sedimentation rates in 1997 and initial dioxin for participants who had normal erythrocyte sedimentation rates in 1982. The percentage of participants who were normal in 1982 and abnormal in 1997 increased as initial dioxin increased.

Table 9-18. Summary of Initial Dioxin Analysis (Model 2) for General Health Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Questionnaire		
Self-perception of Health (D)	NS	ns
Physical Examination		
Appearance of Illness or Distress (D)	ns	ns
Relative Age Appearance (D)	NS	NS
Body Fat (C)	NS*	+0.020
Body Fat (D)	NS	NS
Laboratory		
Erythrocyte Sedimentation Rate (C)	NS	NS
Erythrocyte Sedimentation Rate (D)	NS	NS

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

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

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

9.4.3 Model 3: Categorized Dioxin Analysis

Table 9-19 summarizes the results of the categorized dioxin analyses. More Ranch Hands in the low dioxin category and in the low and high combined Ranch Hand category appeared ill or distressed than did Comparisons, without adjustment for covariates. After adjustment for covariates, the result was marginally significant in the low dioxin category and nonsignificant in the low and high combined Ranch Hand category contrasts.

The unadjusted and adjusted analyses of categorized dioxin yielded similar results for the self-perception of health and body fat (continuous) variables. Significantly more Ranch Hands than Comparisons perceived their health to be fair or poor when the low, high, and low and high combined Ranch Hand dioxin categories were contrasted with Comparisons. For the continuous analyses of body fat, the mean in the background Ranch Hand category was significantly lower than the Comparison mean, and the means in the low, high, and low and high combined Ranch Hand dioxin categories were significantly or marginally significantly higher than the Comparison mean.

Unadjusted and adjusted analyses of body fat in its discrete form revealed a significantly lower percentage of obese Ranch Hands in the background dioxin category, and a marginally significant higher percentage of obese Ranch Hands in the low dioxin category, than Comparisons. In the combined low and high dioxin category, a significantly greater percentage of Ranch Hands than Comparisons were obese; this difference was marginally significant after adjustment for covariates.

All results for categorized dioxin analysis of relative age appearance and the discrete and continuous forms of erythrocyte sedimentation rate were nonsignificant.

Longitudinal analyses revealed significantly more Ranch Hands in the low dioxin category than Comparisons who were normal in 1982, but appeared ill or distressed in 1987. The difference between Ranch Hands in the high dioxin category and Comparisons was not significant.

The percentage of participants with abnormal erythrocyte sedimentation rates in 1997, who were normal in 1982, increased as categorized dioxin increased. Ranch Hands in the high dioxin category had a significantly greater percentage of 1997 erythrocyte sedimentation rate abnormalities than Comparisons, based on both cohorts being normal in 1982.

Table 9-19. Summary of Categorized Dioxin Analysis (Model 3) for General Health 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
Questionnaire				
Self-perception of Health (D)	ns	+0.005	+<0.001	+<0.001
Physical Examination				
Appearance of Illness or Distress (D)	ns	+0.031	NS	+0.041
Relative Age Appearance (D)	NS	NS	NS	NS
Body Fat (C)	–<0.001	+0.045	0.001	<0.001
Body Fat (D)	–<0.001	NS*	ns	+0.042
Laboratory				
Erythrocyte Sedimentation Rate (C)	ns	NS	NS	NS
Erythrocyte Sedimentation Rate (D)	NS	NS	NS	NS

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

P-value given if p≤0.05.

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

Table 9-19. Summary of Categorized Dioxin Analysis (Model 3) for General Health Variables (Ranch Hands vs. Comparisons) (Continued)

	ADJUSTED			
Variable	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Questionnaire				
Self-perception of Health (D)	NS	+0.020	+0.002	+0.001
Physical Examination				
Appearance of Illness or Distress (D)	ns	NS*	NS	NS
Relative Age Appearance (D)	NS	NS	NS	NS
Body Fat (C)	–<0.001	NS*	0.001	0.001
Body Fat (D)	–0.001	NS*	NS	NS*
Laboratory				
Erythrocyte Sedimentation Rate (C)	ns	NS	NS	NS
Erythrocyte Sedimentation Rate (D)	NS	NS	NS	NS

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

P-value given if p≤0.05.

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

9.4.4 Model 4: 1987 Dioxin Level Analysis

Several significant associations between the measures of general health studied in this assessment and the 1987 dioxin level associations were found, as presented in Table 9-20. Each of the unadjusted analyses of associations of 1987 dioxin levels and self-perception of health, body fat (continuous and discrete forms), and erythrocyte sedimentation rate (continuous and discrete forms) were significant. For these significant associations, discrete analyses produced relative risks greater than 1.0, and continuous analyses showed an increase in body fat and erythrocyte sedimentation rate as 1987 dioxin levels increased. After covariate adjustments, results remained significant for the body fat (continuous and discrete) adjusted analyses. The adjusted analysis of erythrocyte sedimentation rate in its continuous form also remained significant in the adjusted analysis, but the result was nonsignificant for the discrete adjusted analysis. The association between 1987 dioxin levels and self-perception of health became marginally significant. Associations were nonsignificant for both unadjusted and adjusted analyses of appearance of illness or distress and relative age appearance.

Table 9-20. Summary of 1987 Dioxin Analysis (Model 4) for General Health Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Questionnaire		
Self-perception of Health (D)	+0.002	NS*
Physical Examination		
Appearance of Illness or Distress (D)	NS	NS
Relative Age Appearance (D)	ns	ns
Body Fat (C)	+<0.001	+<0.001
Body Fat (D)	+<0.001	+<0.001
Laboratory		
Erythrocyte Sedimentation Rate (C)	+0.004	+0.037
Erythrocyte Sedimentation Rate (D)	+0.040	NS

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

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

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

9.5 CONCLUSION

The self-perception of health analysis revealed significant differences among Ranch Hands and Comparisons, with more Ranch Hands than Comparisons indicating their health as fair or poor. As in previous examinations, the difference was most apparent in enlisted groundcrew, who had the highest average dioxin levels. This observation also was confirmed in the categorized dioxin analysis, where Ranch Hands with the highest dioxin levels perceived their health as fair or poor more often than Comparisons. Also, among Ranch Hands, those with the higher 1987 dioxin levels reported fair or poor health more often than Ranch Hands with lower levels. These results are consistent with the 1985, 1987, and 1992 examinations. No group differences were noted in the appearance of illness or relative age, as recorded by examining physicians, nor were these variables correlated with serum dioxin levels in the Ranch Hand cohort.

The analysis of body fat indicated positive associations with dioxin levels. The results of the 1997 examination confirmed those of the 1992 examination and appear consistent with a difference in dioxin pharmacokinetics in obese versus lean individuals.

No differences in the percentages of abnormal erythrocyte sedimentation rates between Ranch Hands and Comparisons or relations between abnormal erythrocyte sedimentation rates and dioxin levels were observed during the 1997 examination. Erythrocyte sedimentation rates increased as 1987 dioxin levels increased.

Longitudinal analyses showed that Ranch Hands, particularly the two enlisted strata, had an increased percentage of abnormal erythrocyte sedimentation rates than did Comparisons over the 15 years of the study since 1982. These analyses also showed that the percentages of abnormalities increased from 1982 to 1997 as dioxin levels increased. This result was seen at the 1987 study, but not in 1992. This positive association raises the possibility of a subtle inflammatory, infectious, or occult malignant disease process related to the body burden of dioxin.

In conclusion, fair or poor self-perception of health displayed an adverse association with dioxin, but the relation with other health conditions is unknown. Increased body fat was associated with increased levels of dioxin exposure, a finding most likely related to the pharmacokinetics of dioxin elimination. Longitudinal analyses indicate an increased percentage of abnormal erythrocyte sedimentation rates in Ranch Hands over Comparisons in the 15 years of the AFHS, and a relation between abnormal erythrocyte sedimentation rates and levels of dioxin during these 15 years. Other measures of general health revealed no association with levels of dioxin.

REFERENCES

1. Institute of Medicine. 1994. *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam.* National Academy Press: Washington, DC.

2. Institute of Medicine. 1996. *Veterans and Agent Orange: Update 1996.* National Academy Press: Washington, DC.

3. Kancir, C. B., C. Andersen, and A. S. Olesen. 1988. Marked hypocalcemia in a fatal poisoning with chlorinated phenoxy acid derivatives. *Clinical Toxicology* 26:257-64.

4. Flanagan, R. J., T. J. Meredith, M. Ruprah, L. J. Onhon, and A. Liddle. 1990. Alkaline diuresis for acute poisoning with chlorophenoxy herbicides and ioxynil. *Lancet* 335:454-8.

5. 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.

6. Lathrop, G. D., S. G. Machado, T. G. Karrison, 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.

7. Thomas, W. F., W. D. Grubbs, T. G. Karrison, M. B. Lustik, R. H. Roegner, D. E. Williams, W. H. Wolfe, J. E. Michalek, J. C. Miner, and R. W. Ogershok. 1990. An epidemiologic investigation of health effects in Air Force personnel following exposure to herbicides: I. 1987 followup examination results, May 1987 to January 1990. NTIS: AD A 222 573. United States Air Force School of Aerospace Medicine, Human Systems Division (AFSC), Brooks Air Force Base, Texas.

8. 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.

9. 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.

10. Visintainer, P. F., M. Barone, H. McGee, and E. L. Peterson. 1995. Proportionate mortality study of Vietnam-era veterans of Michigan. *Journal of Occupational and Environmental Medicine* 37:423-8.

11. Centers for Disease Control. 1989. Health status of Vietnam veterans. Vietnam Experience Study. Atlanta: U.S. Department of Health and Human Services. Vols. I-V, Supplements A-C.

12. Centers for Disease Control. 1990. The Association of Selected Cancers with Service in the U.S. Military in Vietnam: Final Report, Atlanta: U.S. Department of Health and Human Services.

13. Dalager, N. A., H. K. Kang, and T. L. Thomas. 1995. Cancer mortality patterns among women who served in the military: the Vietnam experience. *Journal of Occupational and Environmental Medicine* 37:298-305.

14. Bullman, T. A., K. K. Watanabe, and H. K. Kang. 1994. Risk of testicular cancer associated with surrogate measures of Agent Orange exposure among Vietnam veterans of the Agent Orange Registry. *Annals of Epidemiology* 4:11-6.

15. Wolfe, W. H., J. E. Michalek, J. C. Miner, A. Rahe, J. Silva, W. F. Thomas, W. D. Grubbs, M. B. Lustik, T. G. Karrison, 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.

16. 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* 324:212-8.

17. Asp, S., V. Riihimaki, S. Hernberg, and E. Pukkala. 1994. Mortality and cancer morbidity of Finnish chlorophenoxy herbicide applicators: an 18-year prospective followup. *American Journal of Industrial Medicine* 26:243-53.

18. Bueno de Mesquita, H. B., G. Doornbos, D. A. Van der Kuip, M. Kogevinas, and R. Winkelmann. 1993. Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in the Netherlands. *American Journal of Industrial Medicine* 23:289-300.

19. Saracci, R., M. Kogenvinas, P. A. Bertazzi, B. H. Bueno de Mesquita, D. Coggon, L. M. Green, T. Kauppinen, K. A. L'Abbe, M. Littorin, E. Lynge, J. D. Mathews, M. Neuberger, J. Osman, N. Pearce, and R. Winkelmann. 1991. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. *Lancet* 38:1027-32.

20. Coggon, D., B. Pannett, and P. Winter. 1991. Mortality and incidence of cancer at four factories making phenoxy herbicides. *British Journal of Industrial Medicine* 48:173-8.

21. Eriksson, M., and L. Hardell. 1991. New experiences strengthen the connection between dioxins, phenoyxy acids and malignant tumors. *Lakartidningen* 88:2210-1.

22. Eriksson, M., L. Hardell, H. Malker, and J. Weiner. 1992. Malignant lymphoproliferative diseases in occupations with potential exposure to phenoxyacetic acid or dioxins: a register-based study. *American Journal of Industrial Medicine* 22:305-12.

23. Manz, A., J. Berger, J. H. Dwyer, D. Flesch-Janys, S. Nagel, and H. Waltsgott. 1991. Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 338:959-64.

24. Eriksson, M., L. Hardell, and H. O. Adami. 1990. Exposure to dioxins as a risk factor for soft tissue sarcoma: A population-based case-control study. *Journal of the National Cancer Institute* 82:486-90.

25. Kogevinas, M., R. Saracci, P. A. Bertazzi, B. H. Bueno de Mesquita, D. Coggon, L. M. Green, T. Kauppinen, M. Littorin, E. Lynge, J. D. Mathews, M. Neuberger, J. Osman, N. Pearce, and R. Winkelmann. 1992. Cancer mortality from soft-tissue sarcoma and malignant lymphomas in an international cohort of workers exposed to chlorophenoxy herbicides and chlorophenols. *Chemosphere* 25:1071-6.

26. Kogevinas, M., T. Kauppinen, R. Winkelmann, H. Becher, P. A. Bertazzi, B. Bas, D. Coggon, D. Green, E. Johnson, M. Littorin, E. Lynge, D. A. Marlow, J. D. Mathews, M. Neuberger, T. Benn, B. Pannett, N. Pearce, and R. Saracci. 1995. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols and dioxins: two nested case-control studies. *Epidemiology* 6:396-402.

27. Hardell, L., M. Eriksson, and A. Degerman. 1994. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. *Cancer Research* 54:2386-9.

28. Calvert, G. M., M. H. Sweeney, M. A. Fingerhut, R. W. Hornung, and W. E. Halperin. 1994. Evaluation of porphyria cutanea tarda in U.S. workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *American Journal of Industrial Medicine* 25:559-71.

29. Collins, J. J., M. E. Strauss, G. J. Levinskas, and P. R. Conner. 1993. The mortality experience of workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin in a trichlorophenol-process accident. *Epidemiology* 4:7-13.

30. Assennato, G., D. Cervino, E. A. Emmett, G. Longo, and F. Merlo. 1989. Followup of subjects who developed chloracne following TCDD exposure at Seveso. *American Journal of Industrial Medicine* 16:119-25.

31. Assennato, G., P. Cannatelli, E. Emmett, I. Ghezzi, and F. Merlo. 1989. Medical monitoring of dioxin clean-up workers. *American Industrial Hygiene Association Journal* 50:586-92.

32. Bertazzi, P. 1991. Long-term effects of chemical disasters. Lessons and results from Seveso. *Science of the Total Environment* 106:5-20.

33. Bertazzi, P. A., A. C. Pesatori, D. Consonni, A. Tironi, M. T. Landi, and C. Zocchetti. 1993. Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. *Epidemiology* 4:398-406.

34. Mocarelli, P., A. Marocchi, P. Brambilla, P. Gerthoux, L. Colombo, A. Mondonico, and L. Meazza. 1991. Effects of dioxin exposure in humans at Seveso, Italy. Banbury Report 35 (Biological Basis for Risk Assessment of Dioxins and Related Compounds): 95-110.

35. Zober, A., P. Messerer, and P. Huber. 1990. Thirty-four-year mortality followup of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. *International Archives of Occupational and Environmental Health* 62:139-57.

36. Zober, M. A., M. G. Ott, O. Papke, K. Senft, and C. Germann. 1992. Morbidity study of extruder personnel with potential exposure to brominated dioxins and furans. I. Results of blood monitoring and immunological tests. *British Journal of Industrial Medicine* 49:532-44.

37. Zober, A., M. G. Ott, and P. Messerer. 1994. Morbidity followup study of BASF employees exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after a 1953 chemical reactor incident. *Occupational and Environmental Medicine* 51:479-86.

38. Information Ventures, Inc. 1992. Review of literature on herbicides, including phenoxy herbicides and associated dioxins. Vol. XX: Analysis of recent literature on health effects, and Vol. XX: Annotated bibliography of recent literature on health effects. U.S. Veterans Administration, Dept. of Medicine and Surgery, Washington, DC.

39. Information Ventures, Inc. 1993. Review of literature on herbicides, including phenoxy herbicides and associated dioxins. Vol. XXI: Analysis of recent literature on health effects, and Vol. XXII: Annotated bibliography of recent literature on health effects. U.S. Veterans Administration, Dept. of Medicine and Surgery, Washington, DC.

40. Information Ventures, Inc. 1994. Review of literature on herbicides, including phenoxy herbicides and associated dioxins. Vol. XXIII: Analysis of recent literature on health effects, and Vol. XXIV: Annotated bibliography of recent literature on health effects. U.S. Veterans Administration, Dept. of Medicine and Surgery, Washington, DC.

41. Poland, A., and J. C. Knutson. 1982. 2,3,7,8-Tetrachlorodibenzo-p-dioxin and related halogenated aromatic hydrocarbons: Examination of the mechanism of toxicity. *Annual Review of Pharmacology and Toxicology* 22:517-54.

42. Denison, M. S., L. M. Vella, and A. B. Okey. 1986. Structure and function of the Ah receptor for 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Journal of Biological Chemistry* 261:3987-95.

43. Okey, A. B., D. S. Riddick, and P. A. Harper. 1994. The Ah receptor: Mediator of toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. *Toxicology Letters* 70:1-22.

44. Denison, M. S. 1992. Heterogeneity of rat hepatic Ah receptor: identification of two receptor forms which differ in their biochemical properties. *Journal of Biochemical Toxicology* 7:249-56.

45. Roa, V. R. 1991. Molecular mechanism of action of dioxin-implications of its carcinogenic potency estimation. *Toxic Substances Journal* 8:335-51.

46. Huff, J., G. Lucier, and A. Tritscher. 1994. Carcinogenicity of TCDD: experimental, mechanistic, and epidemiologic evidence. *Annual Review of Pharmacology and Toxicology* 34:343-72.

47. Neubert, D. 1992. Evaluation of toxicity of TCDD in animals as a basis for human risk assessment. *Toxic Substances Journal* 12:237-76.

48. Birnbaum, L. S. 1993. EPA's reassessment of dioxin risk: directed health research. *Chemosphere* 27:469-75.

49. Dickson, L. C., and S. C. Buzik. 1993. Health risks of "dioxins:" a review of environmental and toxicological considerations. *Veterinary and Human Toxicology* 35:68-77.

50. Houk, V. N. 1992. Review of research on health effects of PCDDs and PCDFs to develop human risk assessment. *Toxic Substances Journal* 12:181-90.

51. Roberts, E. A., K. C. Johnson, P. A. Harper, and A. B. Okey. 1990. Characterization of the Ah receptor mediating aryl hydrocarbon hydroxylase induction in the human liver cell line Hep G2. *Archives of Biochemistry and Biophysics* 276:442-50.

52. Waithe, W., M. Michaud, P. Harper, A. Okey, and A. Anderson. 1991. The Ah receptor, cytochrome P450IA1 mRNA induction, and aryl hydrocarbon hydroxylase in a human lymphoblastoid cell line. *Biochemical Pharmacology* 41:85-92.

53. Lorenzen, A., and A. B. Okey. 1991. Detection and characterization of Ah receptor in tissue and cells from human tonsils. *Toxicology and Applied Pharmacology* 107:203-14.

54. Lucier, G. W. 1991. Humans are sensitive species to some of the biochemical effects of structural analogs of dioxin. *Environmental Toxicology and Chemistry* 10:727-35.

55. Wang, X., M. Santostefano, Y. Lu, and S. Safe. 1992. A comparison of the mouse versus human aryl hydrocarbon (Ah) receptor complex: effects of proteolysis. *Chemico-Biological Interactions* 85:79-93.

56. Wang, X., R. Rosengren, V. Morrison, and S. Safe. 1992. Characterization of the human Ah receptor. *Chemosphere* 25:997-1000.

57. Patterson, D. G., L. Hampton, L. C. R. Lapeza Jr., W. T. Belser, V. Green, L. Alexander, and L. L. Needham. 1987. High resolution gas chromatographic/high-resolution mass spectrometric analysis of human serum on a whole-weight and lipid basis for 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Analytical Chemistry* 59:2000-5.

58. 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.

59. Needham, L. L., P. M. Gerthoux, D. G. Patterson, P. Brambilla, J. L. Pirkle, P. I. Tramaccre, W. E. Turner, C. Beretta, E. J. Sampson, and P. Mocarelli. 1994. Half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in serum of Seveso adults: interim report. *Organohalogen Compounds* 21:81-5.

60. Flesch-Janys, D., P. Gurn, D. Jung, J. Konietzke, and O. Papke. 1994. First results of an investigation of the elimination of polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/F) in occupationally exposed persons. *Organohalogen Compounds* 21:93-9.

61. Michalek, J. E., R. C. Tripathi, P. M. Kulkarni, and J. L. Pirkle. 1996. The reliability of the serum dioxin measurement in veterans of Operation Ranch Hand. *Journal of Exposure Analysis and Environmental Epidemiology* 6:327-38.

62. Michalek, J. E., R. Tripathi, S. Caudill, and J. L. Pirkle. 1992. Investigation of TCDD half-life heterogeneity in veterans of Operation Ranch Hand. *Journal of Toxicology and Environmental Health* 35:29-38.

63. U.S. Centers for Disease Control (USCDC). 1988. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in US Army Vietnam-Era veterans. *Journal of the American Medical Association* 260:1249-54.

64. Kang, H. K., K. K. Watanabe, J. Breen, J. Remmers, M. G. Conomos, J. Stanley, and M. Flicker. 1991. Dioxins and dibenzofurans in adipose tissue of US Vietnam veterans and controls. *American Journal of Public Health* 813:344-9.

65. Michalek, J. E., W. H. Wolfe, J. C. Miner, T. M. Papa, and J. L. Pirkle. 1995. Indices of TCDD exposure and TCDD body burden in Veterans of Operation Ranch Hand. *Journal of Exposure Analysis and Environmental Epidemiology* 5:209-23.

66. Fingerhut, M. A., M. H. Sweeney, D. G. Patterson Jr., L. A. Piacitelli, J. A. Morris, D. A. Marlow, R. W. Hornung, L. W. Cameron, L. B. Connally, L. L. Needham, and W. E. Halperin. 1989. Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the serum of U.S. chemical workers exposed to dioxin contaminated products: Interim results. *Chemosphere* 19:835-40.

67. Schecter, A., H. McGee, J. Stanley, and K. Boggess. 1992. Dioxin, dibenzofuran, and PCB, including coplanar PCB levels in the blood of Vietnam veterans in the Michigan Agent Orange Study. *Chemosphere* 24:205-8.

68. Piacitelli, L. A., M. H. Sweeney, M. A. Fingerhut, D. G. Patterson, W. E. Turner, L. B. Connally, K. K. Wille, and B. Tompkins. 1992. Serum levels of PCDDs and PCDFs among workers exposed to 2,3,7,8-TCDD contaminated chemicals. *Chemosphere* 25:251-4.

69. Pirkle, J., and V. Houk. 1992. Use of epidemiologic studies to assess human risk from exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Chemosphere* 25:1109-16.

70. Sweeney, M. H., M. A. Fingerhut, D. G. Patterson Jr., L. B. Connally, L. A. Piacitelli, J. A. Morris, A. L. Greife, R. W. Hornung, D. A. Marlow, J. E. Dugle, W. E. Halperin, and L. L. Needham. 1990. Comparison of serum levels of 2,3,7,8-TCDD in TCP production workers and in an unexposed comparison group. *Chemosphere* 20:993-1000.

71. Ott, M. G., P. Messerer, and A. Zober. 1993. Assessment of past occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin using blood lipid analyses. *International Archives of Occupational and Environmental Health* 65:1-8.

72. Zober, A., and O. Papke. 1993. Concentrations of PCDDs and PCDFs in human tissue 36 years after accidental dioxin exposure. *Chemosphere* 27:413-8.

73. Flesch-Janys, D., J. Berger, J. Konietzko, A. Manz, S. Nagel, and J. Wahrendorf. 1992. Quantification of exposure to dioxins and furans in a cohort of workers of an herbicide producing plant in Hamburg, FRG. *Chemosphere* 25:1021-8.

74. Schecter, A., J. J. Ryan, O. Papke, M. Ball, and A. Lis. 1993. Elevated dioxin levels in the blood of male and female Russian workers with and without chloracne 25 years after phenoxyherbicide exposure: The UFA "Khimprom" incident. *Chemosphere* 27:253-8.

75. Fedorov, L. A. 1993. Dioxin problem in Russian chemical industry. *Chemosphere* 27:477-81.

76. Smith, A., D. J. Patterson, M. Warner, R. MacKenzie, and L. Needham. 1992. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels of New Zealand pesticide applicators and their implication for cancer hypotheses. *Journal of the National Cancer Institute* 84:104-8.

77. Neuberger, M., W. Landvoigt, and F. Derntl. 1991. Blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in chemical workers after chloracne and in comparison groups. *International Archives of Occupational and Environmental Health* 63:325-8.

78. Johnson, E. W., W. Parsons, C. R. Weinberg, D. L. Shore, J. Mathews, D. G. Patterson, and L. L. Needham. 1992. Current serum levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in phenoxy acid herbicide applicators and characterization of historical levels. *Journal of the National Cancer Institute* 84:1648-53.

79. Mocarelli, P., L. L. Needham, A. Marocchi, D. G. Patterson Jr., P. Brambilla, P. M. Gerthoux, L. Meazza, and V. Carreri. 1991. Serum concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin and test results from selected residents of Seveso, Italy. *Journal of Toxicology and Environmental Health* 32:357-66.

80. 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.

81. Sweeney, M. H., M. A. Fingerhut, J. C. Arezzo, R. W. Hornung, and L. B. Connally. 1993. Peripheral neuropathy after occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *American Journal of Industrial Medicine* 23:845-58.

82. Peper, M., M. Klett, R. Frentzel-Beyme, and W. D. Heller. 1993. Neuropsychological effects of chronic exposure to environmental dioxins and furans. *Environmental Research* 60:124-35.

83. Patterson Jr., D. G., M. A. Fingerhut, D. W. Roberts, L. L. Needham, M. H. Sweeney, D. A. Marlow, J. S. Andrews Jr., and W. E. Halperin. 1989. Levels of polychlorinated dibenzo-p-dioxins and dibenzofurans in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *American Journal of Industrial Medicine* 16:135-46.

84. 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.

85. 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.

86. Mausner, J. S., and A. K. Bahn. 1974. *Epidemiology – An Introductory Text.* Philadelphia: W. B. Saunders Company.

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10 NEOPLASIA ASSESSMENT

10.1 INTRODUCTION

10.1.1 Background

Between 1977 and 1988, numerous long-term exposure studies established the multi-organ carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) in experimental animals (1-8). The oncogenic response to dioxin occurs in multiple strains and species, in both sexes, and by several routes of administration: dermal (5), feeding (1, 2) and gavage (3, 4, 6), and intraperitoneal injection (7). Across a wide dose range and duration of exposure, dioxin can be considered a "complete" carcinogen solely responsible for a variety of malignant tumors at multiple sites (9). In rats, it has produced tumors of the liver, thyroid, adrenal cortex, lung, nasopharynx, tongue, brain, kidney, and breast (1, 2, 4); in mice, tumors of the liver, thymus, breast, stomach, and skin (3-6); and in the Syrian Hamster, a squamous cell carcinoma of the skin (7). The histopathologic characteristics of the neoplastic response demonstrated even greater variety—more than 30 distinct malignancies have been characterized microscopically (10).

As summarized in a recent review article (11), much of the basic research into the carcinogenicity of dioxin in laboratory animals has focused on the properties of the aryl hydrocarbon (Ah) receptor and the induction of the cytochrome P-450 enzyme system (11-17). The biologic basis for the assessment of risk related to dioxin exposure has been well established in molecular, biochemical, and pharmacologic studies and reviews (13, 18-24). The Ah receptor has been isolated from the tissues of several human organs (25-28) and the comparative properties of animal and human receptors have been studied (29, 30). These experiments have demonstrated far fewer Ah receptor sites and a significant reduction in dioxin binding affinity in human cells relative to rodent cell lines. These results suggest that at any level of exposure, humans may be less at risk for dioxin toxicity than laboratory animals (24).

Despite the conclusive evidence that dioxin is a potent carcinogen in animal experiments, the carcinogenicity of dioxin in humans remains controversial (31-36). The limitations of most epidemiological studies are well recognized and include the recall bias inherent in the retrospective collection of data, confounding by exposure to other potential toxins, histologic misclassification, and the lack of accurate indices of prior exposure to dioxin (31, 37, 38). Despite these limitations, the Institute of Medicine has concluded that there is "sufficient" evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of soft tissue sarcoma (STS), non-Hodgkin's lymphoma, and Hodgkin's disease. The evidence for an association with respiratory cancers, prostate cancer, and multiple myeloma was considered "limited/suggestive" (39). Each of these malignancies is among the clinical endpoints included in mortality and morbidity data collected in this and previous examinations of the Air Force Health Study (AFHS).

Most of the longitudinal studies of dioxin toxicity have included malignancy as a clinical endpoint and have been based on cohorts of veterans who served during the Vietnam era (40-49) and of civilian populations exposed to dioxin by occupation (50-59) or as a consequence of industrial accidents (60-64). The development of assay techniques that quantitate the tissue concentration of dioxin in parts per quadrillion (65) and the validation of the reproducibility and reliability of the serum dioxin assay in parts per trillion (ppt) (66) have placed epidemiological studies of dioxin toxicity on a much more scientific footing. The serial analysis of serum dioxin levels from specimens taken 15 to 25 years after exposure has demonstrated that the best estimate for the half-life of dioxin in humans is 8.7 years (67). Although an increasing number of published studies have incorporated serum dioxin levels into their analyses (68-73), few have examined the incidence of malignancy and associated mortality in relation to this index of dioxin exposure (44, 50, 52, 59, 60, 63).

As part of the National Institute of Occupational Safety and Health's (NIOSH) Dioxin Registry, cause-specific mortality was determined in 5,172 workers exposed to dioxin at chemical production plants (50). The mean dioxin level of 253 members of the exposed cohort was 233 ppt versus 7 ppt in the unexposed cohort. In the entire group of exposed workers, there was a slight but statistically significant increase in mortality from all cancers combined but not from those associated with dioxin exposure (non-Hodgkin's lymphoma, Hodgkin's disease, and STS). In a subcohort of 1,520 workers with longer exposure (greater than 1 year; mean serum dioxin of 418 ppt) and greater latency (more than 20 years since first exposure), there was a further increase in the mortality from all cancers combined (15% excess), a 42 percent excess of respiratory cancers, and a ninefold excess of STS sarcoma (35). In the most recently published report from the NIOSH study, which extended the period of observation for another 6 years through 1993, the standardized mortality ratio for all cancers combined in the cohort with the highest exposure was 1.60 and for lung cancer, 1.65 (74).

Although methodological limitations of the NIOSH study such as tissue classification (75), confounding (34, 61), and others (10) have been commented upon in the literature, some of the results are consistent with those of several other occupational epidemiological studies from Germany. In a 34-year follow-up of German factory workers exposed during a chemical explosion in 1953, the increase in mortality from all cancers combined was statistically significant only after a latency period of greater than 20 years (63). Similarly, in another mortality study of herbicide production workers who were followed over a 32-year period and whose exposure was verified by adipose tissue level (average dioxin level of 296 ng/kg), the increase in all-cancer mortality was significant only in those with more than 1-year exposure and latency period greater than 20 years. In this group, a significant increase in mortality was noted from both lung and hematopoietic cancers with a threefold increase in risk for non-Hodgkin's lymphoma (52). In the most recently published report of this study, the mortality follow-up was extended another 3 years and the significant increase in all-cancer mortality was confirmed (59). Taken together, the NIOSH and German studies are consistent with a carcinogenic effect of dioxin in humans with demonstrable dose-response and latency effects.

By far the most extreme human exposure to dioxin occurred consequent to the industrial explosion at Seveso, Italy, in 1976 (60, 64, 76, 77). In the population closest to the explosion (Zone A), serum levels of dioxin ranged from 828 ppt to 56,000 ppt, the highest ever recorded (78). In the most recent follow-up report published (60), residents of Zone B, farther from the source of contamination with serum dioxin levels ranging from 74 ppt to 526 ppt shortly after the accident, statistically significant increases in several cancers were noted, including primary hepatic and hematopoietic cancers and, particularly, non-Hodgkin's lymphoma in men and, in women, cancers of the gallbladder and biliary tree. The Seveso studies are limited by the small sample sizes (particularly in the group most heavily exposed), the limited data available on serum dioxin levels, and the lack of sufficient latency for the development of cancer.

In the incorporation of serial serum dioxin data into longitudinal analyses, the AFHS is unique among those that have examined the incidence of malignancy in Vietnam War veterans. During the 1992 examinations, after 10 years of observation, the median serum dioxin level in the Ranch Hand cohort was nearly three times that of the Comparison group (12.5 ppt versus 4.1 ppt) (44). Further, stratification of the Ranch Hand cohort by occupation revealed significantly higher median levels of serum dioxin in the enlisted groundcrew (24.1 ppt) and enlisted flyers (17.8 ppt) than in the officers (7.7 ppt).

In the 1992 follow-up examination, Ranch Hands continued to have a slightly higher history of benign and malignant skin neoplasms than Comparisons, but group differences were no longer significant. A statistically significant inverse dose-response effect was noted, as basal cell skin cancer decreased as the level of serum dioxin increased. In contrast to the 1987 examinations, when Ranch Hands were found to have significantly more benign systemic neoplasms relative to Comparisons, in the 1992 examinations, the occurrence of benign systemic neoplasms was similar in each cohort with no evidence for a dose-response effect. There were no significant group differences in the morbidity or mortality associated with any systemic malignancy, nor was there any increased risk associated with current or initial levels of serum dioxin. In a recently published AFHS article, based on data collected through the 1992 examination, there was no significant increase in cancer risk in Ranch Hands with the highest levels of serum dioxin, nor was there any consistent evidence for a dose-response effect (79).

The term "neoplasm" is used throughout this report and refers to any new growth that may or may not be malignant. Malignant neoplasms are those neoplasms capable of invasion and metastasis. Malignant and benign neoplasms, carcinomas in situ, and neoplasms of uncertain behavior or unspecified nature, as well as skin and systemic neoplasms, were studied. "Systemic neoplasm" denotes a nonskin neoplasm.

10.1.2 Summary of Previous Analyses of the Air Force Health Study

10.1.2.1 1982 Baseline Study Summary Results

Cancer received major emphasis during the AFHS baseline examination in 1982. The neoplasia assessment used data from both the in-home questionnaire and the review-of-systems questionnaire obtained during the physical examination, as well as data from the examination itself. All data were verified by a medical records review. In addition, tabulation of mortality count data from the Baseline Mortality Report was used in conjunction with cancer morbidity information. The overall results did not show a significant difference in systemic cancer between the two groups, but did show significantly more skin cancer (p=0.03) in the Ranch Hand group.

Of 50 reported systemic cancers from the Ranch Hand and Comparison groups, 28 (14 in each group) were verified by medical records and pathology reports. A visual inspection of anatomic sites showed a slight excess of genitourinary cancer and oropharyngeal cancer but a relative deficit of digestive system neoplasms in Ranch Hands. A combined morbidity-mortality assessment derived from the initial 1:1 match (Ranch Hand to the Original Comparison member) disclosed similar distributions. One case of STS and one case of Hodgkin's disease were confirmed, both in the Comparison group.

Questionnaire data verified by a medical records review revealed significantly more skin cancer in Ranch Hands (odds ratio 2.35). Basal cell carcinoma accounted for 83.9 percent of the reported skin cancers in both groups and was concentrated anatomically on the face, head, and neck. The few melanoma and squamous cell cancers were distributed evenly between the Ranch Hand and Comparison groups. Skin cancer in both groups was associated with exposure to industrial chemicals (p=0.03). Adjustments for occupational exposures (e.g., asbestos, degreasing chemicals) did not alter the increased rate of skin cancer in the Ranch Hand group. Outdoor occupations subsequent to military service as a covariate did not account for the significant skin cancer association.

10.1.2.2 1985 Follow-up Study Summary Results

The baseline and 1985 follow-up data were combined for the assessment of lifetime history of cancer; occurrences of cancer prior to their service in Southeast Asia (SEA) were excluded.

For the unadjusted analyses (Blacks and non-Blacks included), Ranch Hands had a significantly greater frequency of a verified skin neoplasm (malignant, benign, or uncertain behavior or unspecified nature) than Comparisons. There were no significant unadjusted group differences in non-Black participants for basal cell carcinoma, squamous cell carcinoma, melanoma, or all malignant skin neoplasms. For verified sun exposure-related malignant skin neoplasms, Ranch Hands had a marginally significantly greater frequency than Comparisons. The groups did not differ significantly for verified and suspected sun exposure-related malignant skin neoplasms. The adjusted group contrast for the sun exposure-related skin cancers, the majority of which were basal cell carcinomas, also was significant (p=0.030).

The unadjusted group contrasts for all systemic cancers combined were not significant. There was one new occurrence of an STS (Ranch Hand) and one suspected cancer of the lymphatic system (Ranch Hand), in addition to the one previously reported STS and one Hodgkin's disease in the Comparison group. There were no cases of non-Hodgkin's lymphoma in either group at the time of the 1985 report.

10.1.2.3 1987 Follow-up Study Summary Results

The unadjusted analysis of all verified neoplasms indicated that the proportion of Ranch Hands with a neoplasm was significantly greater than that of Comparisons. After including suspected neoplasms with verified neoplasms, the Ranch Hand proportion was marginally greater than the Comparison proportion. The majority of malignant neoplasms observed in Ranch Hands were basal cell carcinomas, a nonlife-threatening form of skin cancer. When the analysis was performed only on skin neoplasms for non-Black participants, significantly more Ranch Hands had a skin neoplasm than did Comparisons.

In the unadjusted analyses of verified basal cell carcinoma, a marginally significant group difference was found. After adjustment for age, residential history, sun exposure, ethnic background, and ionizing radiation exposure, the Ranch Hand risk was statistically significantly increased for verified basal cell carcinoma. Also, Ranch Hands had a significantly higher percentage of participants with multiple verified basal cell carcinomas than did Comparisons.

Sun exposure-related malignant skin neoplasms also exhibited group differences. (Approximately 90 percent of the participants with a sun exposure-related malignant neoplasm had a basal cell carcinoma.) In both the unadjusted and adjusted analyses, Ranch Hands exhibited a significantly increased risk for these neoplasms.

No significant group differences were found in the analyses of systemic neoplasms by number, behavior (malignant, benign, or uncertain behavior or unspecified nature), or site. Thus, the increase in overall malignancy was because of elevated relative risks for skin cancer (basal cell carcinoma). The number of STS and non-Hodgkin's lymphoma was comparable in the two groups.

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

The analyses generally did not establish a positive association between dioxin and the presence of a skin neoplasm. Significant relative risks were found for the skin neoplasm analyses; although, the relative risks were almost always less than 1.0. For the analyses focusing on enlisted flyers with a basal cell carcinoma of other sites (and a sun exposure-related malignant skin neoplasm of other sites), relative risks were found to be significant and greater than 1.0. These differences were not noted in the enlisted groundcrew who, as a group, had higher levels of serum dioxin than the enlisted flyers.

In general, the analyses of all systemic neoplasms combined produced some significant or marginally significant relative risks greater than 1.0. The relative risk for participants with a benign systemic neoplasm was significantly greater than 1.0. The relative risk of malignant systemic neoplasms was generally not significantly increased with increases in dioxin levels.

The study provided no evidence of increased history of malignant neoplasms most commonly suspected as being associated with exposure to chlorophenols (Hodgkin's disease, non-Hodgkin's lymphoma, and STS). The number of participants with these specific malignancies was small; therefore, the statistical power to detect small or moderately elevated relative risks was low. There is no evidence of a relation between dioxin and either skin or systemic malignancies in these data. There was a suggestion of a dose-response relation between dioxin and benign systemic neoplasms.

10.1.2.5 1992 Follow-up Study Summary Results

Analyses of all Ranch Hands and Comparisons indicated no significant difference between the two groups with regard to benign or malignant neoplasms. All statistically significant associations between initial dioxin and benign or malignant neoplasm endpoints for Ranch Hands showed an inverse dose-response relation. In the categorized dioxin analyses occurrence of neoplasms for Ranch Hands in the background and low dioxin categories was often greater than the occurrence for Comparisons before adjustment for covariates. After adjustment, the only significantly increased risks were for Ranch Hands in the low category (overall skin neoplasms and malignancies of the colon and rectum). In contrast, the occurrence of neoplasms of any type for Ranch Hands in the high dioxin category was never significantly elevated and was often less than the occurrence for Comparisons. Parallel to analyses using initial dioxin, results observed when current dioxin was used as the measure of exposure often indicated a negative dose-response relation, although this was statistically significant in the adjusted analyses only for benign skin neoplasms. In summary, there appeared to be no overall difference between Ranch Hands and Comparisons, and there was no evidence to suggest a positive dose-response relation between dioxin and neoplastic disease.

10.1.3 Parameters for the 1997 Neoplasia Assessment

10.1.3.1 Dependent Variables

The neoplasia assessment was based on the occurrence of neoplasms (both benign and malignant) after service in SEA. Information on the occurrence of neoplasms was indicated in the health questionnaires and the physical examinations at the 1982 baseline examination and at the 1985, 1987, and 1992 follow-up studies and was coded according to conventions in the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) manual. This information was combined with data collected at the 1997 follow-up examination to form a complete neoplastic history for each participant.

The neoplasia assessment was based on the number of participants with a neoplasm and not on the number of neoplasms. A participant was considered to have an adverse health condition for the neoplasia assessment if he had one or more neoplasms.

10.1.3.1.1 Medical Records Data

During the 1997 health interview, each study participant was asked a series of questions on the occurrence of cancer since the date of his last health interview. The self-reported conditions were verified by a medical records review and combined with cancer information collected at previous AFHS examinations. Only verified neoplasms were used in the neoplasia assessment.

Some possible neoplastic conditions were discovered by the physicians at the physical examination. Contingent upon participant authorization, suspicious skin lesions were biopsied and the pathology determined; no other invasive procedures were used to detect systemic neoplasms.

10.1.3.1.1.1 Skin Neoplasms

The analysis of skin neoplasms was divided into two sets. Analysis Set 1 consisted of analyses of skin neoplasms by behavior type. Four behavior types were examined: (1) all skin neoplasms, (2) malignant skin neoplasms only, (3) benign skin neoplasms only, and (4) skin neoplasms of uncertain behavior or unspecified nature.

Analysis Set 2 consisted of analyses of malignant skin neoplasms by cell type. The following four cell types were analyzed: (1) basal cell carcinomas, (2) squamous cell carcinomas, (3) nonmelanoma (basal cell carcinomas, squamous cell carcinomas, and malignant epithelial neoplasms not otherwise specified), and (4) melanoma. Analysis of basal cell carcinomas was conducted for all sites combined and by site. The following four sites were examined for basal cell carcinomas: (1) ear, face, head, and neck; (2) trunk; (3) upper extremities; and (4) lower extremities.

There were relatively few Black participants in this study (approximately 5%). With the exception of one Black participant with a pre-SEA melanoma, Blacks have been observed to exhibit only benign skin neoplasms in all phases of the study to date. Consequently, skin neoplasm analyses, except for the analyses of benign skin neoplasms, were limited to non-Blacks. Both Blacks and non-Blacks were included in the analysis of benign skin neoplasms. Participants with a pre-SEA skin neoplasm were excluded from the analysis of the skin neoplasm variables.

10.1.3.1.1.2 Systemic Neoplasms

The systemic neoplasms were analyzed by behavior and anatomical site. As with skin neoplasms, each analysis was conducted using verified data. The analysis of the systemic neoplasms was divided into two sets, described below.

Analysis Set 1 consisted of analyses of systemic neoplasms by behavior type. The following four behavior types were examined: (1) all systemic neoplasms, (2) malignant systemic neoplasms, (3) benign systemic neoplasms, and (4) systemic neoplasms of uncertain behavior or unspecified nature.

Analysis Set 2 consisted of analyses of malignant systemic neoplasms by the following sites: (1) ear, eye, head, face, and neck; (2) oral cavity, pharynx, and larynx; (3) esophagus; (4) brain; (5) thymus and mediastinum; (6) thyroid gland; (7) bronchus and lung; (8) liver; (9) colon and rectum; (10) kidney and bladder; (11) prostate; (12) testicles; (13) extrahepatic bile duct; (14) ill-defined sites; (15) connective and other soft tissues; and (16) carcinomas in situ of the penis.

In addition to the analyses described above, the number of participants with Hodgkin's disease, non-Hodgkin's lymphoma, and a malignant systemic neoplasm of lymphoid and histiocytic tissue was analyzed.

Participants with a pre-SEA malignant systemic neoplasm or a pre-SEA systemic neoplasm of uncertain behavior or an unspecified nature were excluded from the analysis of the systemic neoplasm variables.

10.1.3.1.1.3 Skin and Systemic Neoplasms

Statistical analysis was performed on all malignant neoplasms, which was a combination of malignant skin and malignant systemic neoplasms. In addition, statistical analysis was performed on all neoplasms, which was a combination of all skin and all systemic neoplasms (benign, malignant, and uncertain behavior). Participants with a pre-SEA skin neoplasm, a pre-SEA malignant systemic neoplasm, or a pre-SEA systemic neoplasm of uncertain behavior or an unspecified nature were excluded from the analysis of this variable.

10.1.3.1.2 Laboratory Examination Data

The prostate-specific antigen (PSA) test was developed to detect prostate enlargement and prostate cancer. Each participant had his PSA measured as a standard part of the laboratory assay. This measurement was continuous in nature, and the units were ng/ml. An analysis was performed on the continuous measurement, as well as on a discrete form. The discrete form of PSA was categorized as high or normal, based on a cutpoint of 4 ng/ml.

10.1.3.2 Covariates

In the analysis of the 1997 examination results, covariates in adjusted statistical analyses assessing skin neoplasms included age, military occupation, skin color, hair color, eye color, skin reaction to sun after the first exposure, skin reaction to sun after repeated exposure, lifetime exposure to ionizing radiation and industrial chemicals (yes or no), and average lifetime residential history. A composite skin-reaction index, which is a composite of the two individual reactions of skin to sun covariates, also was investigated.

Age, race, and military occupation were determined from military records. Information on skin, hair, and eye color was obtained at the 1997 physical examination for participants who did not attend the 1985, 1987, and 1992 examinations, and this information was combined with data from participants who previously provided this information. Information on the skin reaction to sun after the first exposure and after repeated exposure was reported by the participant during the questionnaire phase at the 1997 examination. Also, the participants' lifetime exposures through 1992 to ionizing radiation, industrial chemicals, and herbicides (used in the analysis of systemic neoplasms, discussed below) was updated with information reported in the 1997 questionnaire.

The emphasis on choosing risk factors related to cancer was increased during the 1985 follow-up study and has been emphasized since that time. In particular, the interval health questionnaire was modified to collect information on each geographic location in which a participant lived for more than 12 months. Because ultraviolet light exposure has been acknowledged as the primary cause of basal cell carcinomas, this information was used to compute a cumulative sun-exposure index based on residential history. An average lifetime residential history was estimated by dividing the total degree-years (i.e., the sum of the product of latitude [degrees] and the number of years lived at each residence) from all residences by the total number of residential years reported on questionnaires since 1985. Average lifetime residential history was dichotomized as less than 37 degrees latitude (southerly) or greater than or equal to 37 degrees latitude (northerly), which was the approximate median in previous AFHS examinations.

Covariates in adjusted statistical analyses assessing systemic neoplasms and PSA included age, race, lifetime exposure to ionizing radiation and herbicides, lifetime cigarette smoking history (in pack-years), and lifetime alcohol history (in drink-years).

Lifetime cigarette smoking history was 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.

Each participant was asked about his drinking patterns throughout his lifetime. When a participant's drinking patterns changed, he was asked to describe how his alcohol consumption differed and the duration of time that the drinking pattern lasted. The participant's average daily alcohol consumption was determined for each of the reported drinking pattern periods throughout his lifetime, and an estimate of the corresponding total number of drink-years was derived. One drink-year was the equivalent of drinking 1.5 ounces of an 80-proof alcoholic beverage, one 12-ounce beer, or one 5-ounce glass of wine per day for 1 year.

Almost all Ranch Hands reported herbicide exposure at some point in their lifetime (see Chapter 8, Covariate Associations with Estimates of Dioxin Exposure). Consequently, herbicide exposure in Ranch Hands was of limited use as a risk factor for explaining the presence of a systemic neoplasm. Therefore, many of the Model 2 and Model 4 analyses of systemic neoplasms and PSA, which were based on Ranch Hands only, did not use herbicide exposure as a covariate. Analyses that did not use herbicide exposure as a covariate are specified in footnotes to the table.

Categories of covariates and definitions are summarized below:

- Skin Color: dark, medium, pale, dark peach, and pale peach (classified for analysis purposes as (1) dark, medium, pale, or (2) dark peach, pale peach).
- Hair Color: black, dark brown, light brown, blonde, red, and bald (classified for analysis purposes as (1) black, dark brown, or (2) light brown, blonde, red, bald).
- Eye Color: brown, hazel, green, gray, and blue (classified for analysis purposes as (1) brown, (2) hazel, green, or (3) gray, blue).
- Skin Reaction to Sun After First Exposure: burns painfully, burns, becomes red, and no reaction.
- Skin Reaction to Sun After Repeated Exposure: freckles with no tan, tans mildly, tans moderately, and tans deep brown.
- Composite Skin-Reaction Index: a composite variable based on two reactions of skin to sun exposure variables was defined as follows: (1) burns painfully or freckles with no tan, (2) burns or tans mildly, and (3) all other reactions.
- Average Lifetime Residential History: average latitude less than 37 degrees and average greater than or equal to 37 degrees.
- Exposure to Carcinogens: ionizing radiation, industrial chemicals, and herbicides (yes or no for each). These exposures represent lifetime exposure based on self-reported questionnaire data from the 1997 examination combined with previous examinations.

10.1.4 Statistical Methods

Table 10-1 summarizes the statistical analysis performed for the neoplasia assessment. The first part of this table identifies the dependent variables, covariates, exclusions, and the statistical methods. This information is presented in the following four sections: skin neoplasms, systemic neoplasms, skin and systemic neoplasms combined, and PSA. Data source, data form, and cutpoints are summarized at the end of the table. The second part of the table describes the covariates. A covariate was used in its continuous form whenever possible for all adjusted analyses; if necessary, or if the covariate was inherently discrete (e.g., military occupation), or if a categorized form was needed to develop measures of association with the dependent variable, the covariate was categorized as shown in Table 10-1.

Table 10-1. Statistical Analysis for the Neoplasia Assessment

Dependent Variables

Category	Site	Covariates[a]	Exclusions[b]	Statistical Analysis and Methods
Skin Neoplasms				
Behavior				
All	All Sites Combined	(1)	(a)	U:LR A:LR
Malignant	All Sites Combined	(1)	(a)	U:LR A:LR L:LR
Benign	All Sites Combined	(1)	(b)	U:LR A:LR
Uncertain Behavior or Unspecified Nature	All Sites Combined	(1)	(a)	U:LR,CS A:LR
Cell Type and Site				
Basal Cell Carcinoma	All Sites Combined Ear, Face, Head, and Neck Trunk Upper Extremities Lower Extremities	(1)	(a)	U:LR A:LR
Squamous Cell Carcinoma	All Sites Combined	(1)	(a)	U:LR A:LR
Nonmelanoma	All Sites Combined	(1)	(a)	U:LR A:LR
Melanoma	All Sites Combined	(1)	(a)	U:LR,CS A:LR
Systemic Neoplasms				
Behavior				
All	All Sites Combined	(2)	(c)	U:LR A:LR
Malignant	All Sites Combined	(2)	(c)	U:LR A:LR L:LR
Benign	All Sites Combined	(2)	(c)	U:LR A:LR L:LR
Uncertain Behavior or Unspecified Nature	All Sites Combined	(2)	(c)	U:LR A:LR
Site				
Malignant	Eye, Ear, Face, Head, and Neck	(2)	(c)	U:LR A:LR
Malignant	Oral Cavity, Pharynx, and Larynx	(2)	(c)	U:LR A:LR

Table 10-1. Statistical Analysis for the Neoplasia Assessment (Continued)

Category	Site	Covariates[a]	Exclusions[b]	Statistical Analysis and Methods
Malignant	Esophagus	--	(c)	Descriptive
Malignant	Brain	--	(c)	Descriptive
Malignant	Thymus, Heart, and Mediastinum	(2)	(c)	U:LR,CS A:LR
Malignant	Thyroid Gland	(2)	(c)	U:LR,CS A:LR
Malignant	Bronchus and Lung	(2)	(c)	U:LR,CS A:LR
Malignant	Liver	(2)	(c)	U:LR,CS A:LR
Malignant	Colon and Rectum	(2)	(c)	U:LR A:LR
Malignant	Kidney and Bladder	(2)	(c)	U:LR,CS A:LR
Malignant	Prostate	(2)	(c)	U:LR A:LR
Malignant	Testicles	(2)	(c)	U:LR,CS A:LR
Malignant	Extrahepatic Bile Duct	--	(c)	Descriptive
Malignant	Ill-Defined Sites	--	(c)	Descriptive
Malignant	Connective and Other Soft Tissues	(2)	(c)	U:LR,CS A:LR
Carcinoma In Situ	Penis	--	(c)	Descriptive
Hodgkin's Disease	--	(2)	(c)	U:LR,CS A:LR
Non-Hodgkin's Lymphoma	--	(2)	(c)	U:LR,CS A:LR
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	--	(2)	(c)	U:LR,CS A:LR
Skin and Systemic Neoplasms				
All	All Sites Combined	(3)	(d)	U:LR A:LR

Variable (Units)	Data Form	Cutpoints	Covariates[a]	Exclusions[b]	Statistical Analysis and Methods
<u>Prostate-Specific Antigen</u>					
Prostate-Specific Antigen (ng/ml)	D/C	High: >4 Normal: ≤4	(2)	(e)	U:LR,GLM A:LR,GLM

Dependent Variables (Except for PSA)

Data Source: Review of medical records and verification based on AFHS 1997 follow-up questionnaires and physical examinations, except for PSA, which was measured by Scripps Clinic in 1997.
Data Form: Discrete.
Cutpoints: Yes or No.

[a] Covariates:
(1): age, military occupation, skin color, hair color, eye color, skin reaction to sun after first exposure, skin reaction to sun after repeated exposure, composite skin-reaction index, residential history, ionizing radiation exposure, and industrial chemicals exposure.
(2): age, race, military occupation, ionizing radiation exposure, herbicide exposure, lifetime cigarette smoking history, lifetime alcohol history.
(3): age, race, military occupation, skin color, hair color, eye color, skin reaction to sun after first exposure, skin reaction to sun after repeated exposure, composite skin-reaction index, residential history, ionizing radiation exposure, industrial chemicals exposure, herbicide exposure, lifetime cigarette smoking history, lifetime alcohol history.

[b] Exclusions:
(a): participants with pre-SEA skin neoplasms, Blacks.
(b): participants with pre-SEA skin neoplasms.
(c): participants with pre-SEA uncertain behavior neoplasms, participants with pre-SEA malignant systemic neoplasms.
(d): participants with pre-SEA skin neoplasms, participants with pre-SEA uncertain behavior neoplasms, participants with pre-SEA malignant systemic neoplasms.
(e): participants with a prostatectomy or radiation treatment on the prostate gland.

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
Skin Color	PE	D	Non-Peach: Dark, Medium, Pale Peach: Dark Peach, Pale Peach
Hair Color	PE	D	Black, Dark Brown Light Brown, Blonde, Red, Bald
Eye Color	PE	D	Brown Hazel, Green Gray, Blue
Skin Reaction to Sun After First Exposure	Q-SR	D	Burns Painfully Burns Becomes Red No Reaction
Skin Reaction to Sun After Repeated Exposure	Q-SR	D	Freckles with No Tan Tans Mildly Tans Moderately Tans Deep Brown

Table 10-1. Statistical Analysis for the Neoplasia Assessment (Continued)

Variable (Units)	Data Source	Data Form	Cutpoints
Composite Skin-Reaction Index	Q-SR	D	• Burns Painfully After 2 Hours, or Freckles with No Tan After Repeated Exposure • Burns After 2 Hours, or Tans Mildly After Repeated Exposure • All Other Reactions
Average Lifetime Residential History	Q-SR	D	Latitude <37° Latitude ≥37°
Ionizing Radiation Exposure	Q-SR	D	Yes No
Industrial Chemicals Exposure	Q-SR	D	Yes No
Herbicide Exposure	Q-SR	D	Yes No
Lifetime Cigarette Smoking History (pack-years)	Q-SR	D/C	0 >0-10 >10
Lifetime Alcohol History (drink-years)	Q-SR	D/C	0 >0-40 >40

Abbreviations

Data Source: MIL: Air Force military records
PE: 1997 physical examination
Q-SR: Health questionnaires (self-reported)

Data Form: D: Discrete analysis only
D/C: Discrete and continuous analysis 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 for 2x2 tables)
GLM: General linear models analysis
LR: Logistic regression analysis

Many covariates were available for use in adjusted analyses of skin and systemic neoplasms. In addition, the number of neoplasms was small for many of the dependent variables. The modeling strategy for this clinical area was to include as many covariates as feasible. When the number of participants with a history of a particular neoplasm was too small to support analysis including all covariates, elimination of covariates was necessary to develop and support meaningful analysis. The covariates that were removed from analysis for a given health endpoint and model are specified in footnotes to the table.

Table 10-2 provides a summary of the number of participants with missing covariate data. In addition, the number of participants excluded is provided.

Table 10-2. Number of Participants Excluded or with Missing Data for the Neoplasia Assessment

		Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
Variable	Variable Use	Ranch Hand	Comparison	Initial	1987	Ranch Hand	Comparison
Hair Color	COV	0	2	0	0	0	2
Skin Reaction to Sun after First Exposure	COV	1	0	0	1	1	0
Skin Reaction to Sun after Repeated Exposure	COV	1	0	0	1	1	0
Composite Skin-Reaction Index	COV	1	0	0	1	1	0
Lifetime Cigarette Smoking History	COV	2	1	1	2	2	1
Lifetime Alcohol History	COV	6	2	3	6	6	1
Blacks	EXC	55	73	36	55	55	70
Pre-SEA Skin Neoplasm	EXC	10	11	7	10	10	11
Pre-SEA Malignant Systemic Neoplasm	EXC	5	0	4	5	5	0
Pre-SEA Systemic Neoplasm of Uncertain Behavior	EXC	5	2	3	5	5	2
Prostatectomy or Radiation Treatment on Prostate Gland	EXC	41	61	24	40	40	61

Note: 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.

10.1.4.1 Longitudinal Analysis

Longitudinal analysis of malignant skin neoplasms, malignant systemic neoplasms, and benign systemic neoplasms was conducted to evaluate the association between exposure and the change in neoplasm status between the 1982 baseline examination and the 1997 follow-up examination.

10.2 RESULTS

10.2.1 Dependent Variable-Covariate Associations

The associations between the dependent variables examined in the neoplasia assessment and the covariates used in the adjusted analyses were investigated, and the results are presented in Appendix F, Table F-2. These associations are pairwise between the dependent variable and the covariate and are not adjusted for any other covariates. The exclusions specified in Table 10-1 were used in the dependent variable-covariate associations described below.

Tests of covariate association were conducted for any skin neoplasm and malignant skin neoplasms. Results were similar for both variables. Significant associations with age ($p<0.001$ for both) were found, where older participants displayed a greater history of a skin neoplasm or a malignant skin neoplasm than did younger participants. Significant associations also were found with occupation ($p=0.004$ and $p<0.001$, respectively). More benign or malignant skin neoplasms were found for officers, followed by enlisted flyers, and then enlisted groundcrew. Skin color was associated with skin neoplasms and malignant skin neoplasms ($p<0.001$ and $p=0.003$, respectively). A higher percentage of skin neoplasms was found for participants with peach-colored skin as compared to participants with non-peach-colored skin. A significant association also was found between malignant skin neoplasms and hair color ($p=0.025$). More participants with light brown, blonde, or red hair had malignant skin neoplasms than did participants with black or dark brown hair. Eye color displayed a significant association with both variables ($p=0.026$ and $p=0.023$ for any skin neoplasm and any malignant skin neoplasm, respectively). Participants with brown eyes exhibited the smallest percentage of skin neoplasms.

Significant associations also were found between any skin and malignant skin neoplasms and both sun reaction covariates ($p<0.001$ for each). The percentage of participants with skin neoplasms increased as the levels of sun sensitivity increased for both covariates. In addition, the composite skin-reaction index displayed significant associations with both variables ($p<0.001$ for both). For the skin-reaction index, the skin neoplasms and malignant skin neoplasms increased as the reaction to sun increased. The associations with average lifetime residential history were significant ($p=0.017$ and $p<0.001$, respectively). The occurrence of both types of neoplasms was greater for those participants who had lived in more southerly latitudes than in the northern latitudes. Ionizing radiation exposure also displayed significant associations with both variables ($p=0.002$ and $p=0.031$, respectively). More skin neoplasms and malignant skin neoplasms were observed for those participants who reported exposure to ionizing radiation than for those who did not report exposure.

Results from the covariate association tests for benign skin neoplasms were significant only for skin color ($p=0.025$). Participants with peach-colored skin showed more benign skin neoplasms (24.6%) than did participants with non-peach-colored skin (19.8%).

The covariate association test results for (a) any basal cell carcinoma and (b) basal cell carcinoma of the ear, face, head, or neck were similar. Each variable displayed a significant association with age and occupation ($p<0.001$ for each association). The history of a basal cell carcinoma was higher for older participants and highest for officers. Associations with skin color were also significant for both basal cell carcinoma variables ($p=0.019$ and $p=0.018$, respectively), revealing more basal cell carcinomas for participants with peach-colored skin than for participants with non-peach-colored skin. Hair color also was associated significantly with both variables ($p=0.019$ and $p=0.005$). Participants with lighter hair colors displayed more of the two basal cell carcinoma dependent variables than did participants with darker hair colors. Basal cell carcinoma was significantly associated with eye color ($p=0.034$). The smallest percentage of participants with basal cell carcinoma was for those with brown eyes.

Significant associations with any basal cell carcinoma and basal cell carcinoma of the ear, face, head, or neck also were found for both sun reaction covariates ($p<0.001$ for each). Basal cell carcinomas increased as the levels of sun sensitivity increased. In addition, the composite skin-reaction index displayed significant associations with both covariates ($p<0.001$ for both), where basal cell carcinoma increased as the reaction to sun increased. Significant associations also were found for both variables with the average lifetime residential history ($p<0.001$ for both variables). The occurrence of basal cell carcinoma was greater for participants who had lived in the more southerly latitudes. A significant association with ionizing radiation exposure was found for basal cell carcinoma of the ear, face, head, or neck ($p=0.049$). This association revealed more basal cell carcinomas for participants reporting exposure to ionizing radiation.

Tests of covariate association conducted for basal cell carcinoma on the trunk and basal cell carcinoma on the upper extremities showed similar results. Each variable was associated significantly with age ($p=0.007$ and $p=0.031$, respectively). Older participants had more basal cell carcinomas on the trunk and upper extremities than did younger participants. Occupation was also a significant covariate ($p<0.001$ for both). Officers had more basal cell carcinomas of the trunk or upper extremities. Eye color was associated significantly with basal cell carcinoma of the upper extremities ($p=0.005$). Participants with hazel or green eyes had more basal cell carcinomas.

Significant associations with basal cell carcinoma of the trunk and basal cell carcinoma of the upper extremities were also found for both skin reaction to sun after the first exposure ($p=0.006$ and $p<0.001$, respectively) and skin reaction to sun after repeated exposure ($p<0.001$ for both dependent variables). The occurrence of basal cell carcinomas increased as the sensitivity to sun increased. In addition, the composite skin-reaction index displayed significant associations with both variables ($p<0.001$ for both basal cell carcinoma variables), where basal cell carcinoma of the trunk or upper extremities increased as the sensitivity to sun increased. Significant associations also were found for both basal cell carcinoma variables with average lifetime residential history ($p<0.001$ and $p=0.039$, respectively). Basal cell carcinoma of the trunk or upper extremities was higher for participants who had lived in the more southerly latitudes.

Tests of association for squamous cell carcinoma showed several significant findings. A significant association with age ($p=0.002$) displayed more squamous cell carcinomas for older participants (3.0%) than for younger participants (0.9%). The association with occupation also was significant ($p=0.007$). More squamous cell carcinomas were found for officers (3.3%), then enlisted flyers (1.6%), and enlisted groundcrew (1.2%). The associations with both skin reaction to sun covariates also were significant ($p=0.011$ for reaction after first exposure and $p<0.001$ for reaction after repeated exposure). Both skin reaction to sun covariates displayed more squamous cell carcinomas as skin sensitivity to sun increased. The composite skin-reaction index association with squamous cell carcinoma was significant ($p<0.001$). Squamous cell carcinoma increased as the reaction to sun increased. Squamous cell carcinoma for participants who had lived in the more southerly latitudes had occurred more often than for participants who had lived in the northern latitudes ($p=0.009$).

Several covariates were associated significantly with nonmelanoma. Significantly more nonmelanomas ($p<0.001$) were observed in older participants (20.3%) than in younger participants (9.7%). Nonmelanoma also was associated significantly with occupation ($p<0.001$). Nonmelanoma was highest for officers (20.0%), then enlisted flyers (16.0%), and enlisted groundcrew (11.5%). The significant association between nonmelanoma and skin color ($p=0.003$) displayed more nonmelanoma for participants with peach-colored skin than for participants with non-peach-colored skin (17.1% vs. 11.2%). The association between nonmelanoma and hair color was significant ($p=0.016$). Those participants with lighter hair colors exhibited more nonmelanomas (18.7%) compared to those with darker hair colors (14.4%). A significant association between nonmelanoma and eye color showed a smaller percentage of nonmelanoma in participants with brown eyes ($p=0.039$).

Both skin reaction to sun covariates were significant ($p<0.001$ for both covariates) and showed more nonmelanomas as the skin sensitivity to sun increased. The composite skin-reaction index association with nonmelanoma also was significant ($p<0.001$). Nonmelanoma increased as the reaction to sun increased. Nonmelanomas were significantly greater for participants who had lived in more southerly latitudes ($p<0.001$).

A significant association between melanoma and average lifetime residential history was observed (p=0.008). Melanoma was significantly greater for participants who had lived in more northerly latitudes.

Tests of covariate association for any systemic neoplasm were significant for age (p<0.001), occupation (p=0.008), and herbicide exposure (p=0.003). A history of systemic neoplasms was higher for older participants (37.2%) than for younger participants (21.8%). Officers displayed the largest occurrence of a systemic neoplasm (33.9%), followed by enlisted flyers (31.1%), then enlisted groundcrew (27.1%). In addition, participants reporting exposure to herbicides exhibited more systemic neoplasms (32.7%) compared to those who did not report exposure to herbicides (26.4%).

Several covariates displayed a significant association with malignant systemic neoplasms. Age was significant (p<0.001), with older participants showing more malignant systemic neoplasms (10.2%) than younger participants (2.4%). A significant association between malignant systemic neoplasms and occupation was found (p<0.001), with the largest occurrence in officers (8.6%) and enlisted flyers (8.6%), followed by enlisted groundcrew (4.4%). The association with ionizing radiation exposure also was significant (p=0.004). For participants who had reported exposure to ionizing radiation, 9.5 percent had a malignant systemic neoplasm compared to 5.8 percent of participants who had not reported exposure. The association between malignant systemic neoplasms and herbicide exposure was significant (p=0.004). Participants who had reported being exposed to herbicides had more malignant systemic neoplasms (8.0%) than participants who had not reported being exposed (4.6%). Lifetime cigarette smoking history also was associated significantly with malignant systemic neoplasms (p<0.001). Participants who had smoked the heaviest (in terms of pack-years) had more malignant systemic neoplasms.

Benign systemic neoplasms displayed significant associations with age (p<0.001) and herbicide exposure (p=0.045). Older participants exhibited more benign systemic neoplasms (28.9%) than did younger participants (19.2%). A greater percentage of participants who had reported being exposed to herbicides had more benign systemic neoplasms (26.1%) than those participants who had not reported exposure to herbicides (22.1%).

Covariate association tests with systemic neoplasms of uncertain behavior or unspecified nature revealed a significant result for occupation (p=0.031). Officers displayed the most systemic neoplasms of uncertain behavior or unspecified nature (2.9%), followed by enlisted groundcrew (1.5%), then enlisted flyers (0.9%).

A significant association between age and a malignant systemic neoplasm of the eye, ear, face, head, or neck was found (p=0.035). Older participants had more malignant systemic neoplasms of the eye, ear, face, head, or neck (1.4%) than did younger participants (0.4%).

Tests of covariate association for malignant systemic neoplasms of the oral cavity, pharynx, and larynx were significant for age (p=0.041). Older participants displayed more malignant systemic neoplasms of the oral cavity, pharynx, and larynx (0.9%) than did younger participants (0.1%).

Malignant systemic neoplasms of the bronchus and lung were associated significantly with lifetime cigarette smoking history (p<0.001). Only participants who had smoked the most (>10 pack-years) showed a malignant systemic neoplasm of the bronchus or lung (1.4%).

Several significant results were revealed from the covariate association tests conducted for malignant systemic neoplasms of the kidney and bladder. A significant association with age (p=0.014) showed more malignant systemic neoplasms of the kidney or bladder in older participants (1.3%) than in younger participants (0.2%). The association with lifetime cigarette smoking history was significant ($p<0.001$). Malignant systemic neoplasms of the kidney or bladder increased with smoking. The association with lifetime alcohol history also was significant ($p<0.001$). The greatest percentage of participants with malignant systemic neoplasms of the kidney or bladder was for non-drinkers (3.4%).

Tests of covariate association for malignant systemic neoplasms of the prostate revealed several significant results. Older participants had significantly more ($p<0.001$) malignant systemic neoplasms of the prostate (5.3%) than did younger participants (0.2%). A significant association with occupation ($p=0.002$) revealed more malignant systemic neoplasms of the prostate in officers (4.6%), followed by enlisted flyers (3.3%), then enlisted groundcrew (1.7%). A significant result also was found with ionizing radiation exposure ($p=0.044$). For participants reporting exposure to ionizing radiation, 4.5 percent had a malignant systemic neoplasm of the prostate, compared to 2.6 percent who did not report exposure. Results also were significant for the tests of association with herbicide exposure ($p=0.035$). The percentage of participants reporting exposure to herbicides with malignant systemic neoplasms was 3.7 percent, compared to 2.0 percent who did not report exposure to herbicides. Lifetime cigarette smoking history showed a significant association with malignant systemic neoplasms of the prostate ($p=0.017$). The greatest occurrence of malignant systemic neoplasms of the prostate was for participants who had smoked the most (4.1%).

Covariate association tests conducted for all malignant skin and systemic neoplasms and all skin and systemic neoplasms were similar. Age, race, and occupation each were significant for both variables ($p<0.001$ for each test). Older participants showed more neoplasms for both variables than did younger participants. Skin and systemic neoplasms occurred more often in non-Blacks than in Blacks. Officers showed more skin and systemic neoplasms than did enlisted flyers and enlisted groundcrew. Skin color was associated significantly with both dependent variables ($p<0.001$ for each). Participants with peach-colored skin had more skin and systemic neoplasms than did participants with non-peach-colored skin. The association between hair color and all malignant skin and systemic neoplasms was significant ($p<0.001$). Participants who had lighter hair colors had more malignant skin or systemic neoplasms. Eye color associations for both variables were each significant ($p<0.001$ for both tests). Participants with brown eyes showed the smallest occurrence of a skin or systemic neoplasm.

Significant associations with all malignant skin and systemic neoplasms and all skin and systemic neoplasms also were found for both skin reaction to sun and the composite skin-reaction index covariates ($p<0.02$ for all tests). Skin or systemic neoplasms increased as skin sensitivity to the sun increased. A significant association also was found for all malignant skin and systemic neoplasms with the average lifetime residential history covariate ($p<0.001$). Malignant skin or systemic neoplasms occurred more often for participants who lived in more southerly latitudes. The ionizing radiation exposure and herbicide exposure covariate tests were each significant for both variables ($p<0.02$ for all tests). Participants reporting exposure to either ionizing radiation or herbicides displayed more skin and systemic neoplasms (both malignant systemic neoplasms and all systemic neoplasms combined) than did participants who did not report exposure.

Covariate association tests for both the continuous and discrete forms of PSA were significant for age ($p<0.001$ for PSA in both discrete and continuous forms) and occupation ($p<0.001$, continuous, and $p=0.014$, discrete). PSA levels and the proportion of participants with high PSA levels increased with age. Enlisted groundcrew showed the lowest average levels of PSA and the lowest percentage of participants with high PSA levels.

10.2.2 Exposure Analysis

The following section presents results of the statistical analysis of the dependent variables shown in Table 10-1. Dependent variables were derived from a medical records review and verification and a laboratory measurement of PSA at the 1997 follow-up examination.

Four models were examined for each dependent variable given in Table 10-1. 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 (officers, enlisted flyers, and enlisted groundcrew). As described in Table 2-8 and previous reports, 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 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 was included in this model to account for body-fat-related differences in elimination rate (80).

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 to determine the dioxin level. If a participant did not have a 1987 or a 1992 dioxin measurement, the 1997 measurement was used to determine the dioxin level.

Some participants had multiple neoplasms, and a participant may be represented in more than one table; therefore, totals added across tables may not agree. For example, 496 of the 2,121 participants in this study (29.8%) had at least two neoplasms and 94 (10.8%) had at least two malignant neoplasms.

10.2.2.1 Medical Records Review

10.2.2.1.1 Skin Neoplasms (All Sites Combined)

Significant group differences were found for all occupations combined and within the officer and enlisted flyer occupational strata in both the Model 1 unadjusted and adjusted analyses of a history of skin neoplasms (Table 10-3(a,b): Est. RR=1.29, p=0.007; Adj. RR=1.32, p=0.005, for all occupations; Est. RR=1.36, p=0.034; Adj. RR=1.38, p=0.030, for officers; and Est. RR=1.64, p=0.040; Adj. RR=1.66, p=0.040, for enlisted flyers). Each contrast displayed more Ranch Hands than Comparisons with skin neoplasms. Results were nonsignificant for the enlisted groundcrew contrasts (p>0.33 for both the unadjusted and adjusted analyses).

Table 10-3. Analysis of Skin Neoplasms

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

Occupational Category	Group	n	Number (%) Yes	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***805***	***325 (40.4)***	***1.29 (1.07,1.55)***	***0.007***
	Comparison	***1,168***	***402 (34.4)***		
Officer	Ranch Hand	329	150 (45.6)	1.36 (1.02,1.81)	0.034
	Comparison	480	183 (38.1)		
Enlisted Flyer	Ranch Hand	140	56 (40.0)	1.64 (1.02,2.63)	0.040
	Comparison	173	50 (28.9)		
Enlisted Groundcrew	Ranch Hand	336	119 (35.4)	1.12 (0.84,1.50)	0.433
	Comparison	515	169 (32.8)		

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	***1.32 (1.09,1.60)***	***0.005***
Officer	1.38 (1.03,1.85)	0.030
Enlisted Flyer	1.66 (1.02,2.69)	0.040
Enlisted Groundcrew	1.16 (0.86,1.56)	0.339

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

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Number (%) Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	138	63 (45.7)	0.78 (0.67,0.91)	0.001
Medium	150	64 (42.7)		
High	151	42 (27.8)		

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

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

Table 10-3. Analysis of Skin Neoplasms (Continued)

(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (Initial Dioxin)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
439	0.81 (0.68,0.98)	0.028

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

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED				
Dioxin Category	n	Number (%) Yes	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,133	389 (34.3)		
Background RH	359	155 (43.2)	1.49 (1.17,1.90)	0.001
Low RH	210	94 (44.8)	1.54 (1.14,2.07)	0.005
High RH	229	75 (32.8)	0.91 (0.67,1.23)	0.546
Low plus High RH	439	169 (38.5)	1.17 (0.93,1.47)	0.183

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

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

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED			
Dioxin Category	n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
Comparison	1,131		
Background RH	358	1.46 (1.13,1.88)	0.004
Low RH	210	1.49 (1.10,2.04)	0.011
High RH	229	1.05 (0.76,1.45)	0.747
Low plus High RH	439	1.25 (0.98,1.58)	0.073

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

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

Table 10-3. Analysis of Skin Neoplasms (Continued)

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED				
1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)	
1987 Dioxin	n	Number (%) Yes	Estimated Relative Risk (95% C.I.)[a]	p-Value
Low	273	114 (41.8)	0.88 (0.80,0.97)	0.012
Medium	256	120 (46.9)		
High	269	90 (33.5)		

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

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

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (1987 Dioxin + 1)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
797	0.92 (0.82,1.03)	0.147

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

Results from both the unadjusted and adjusted Model 2 analyses indicated a significant inverse relation between initial dioxin and skin neoplasms (Table 10-3(c,d): Est. RR=0.78, p=0.001; Adj. RR=0.81, p=0.028, respectively). As initial dioxin in Ranch Hands increased, the occurrence of skin neoplasms decreased.

The Model 3 analyses contrasting Ranch Hands in both the background dioxin category and low dioxin category with Comparisons displayed significant results in the unadjusted and adjusted analyses of skin neoplasms (Table 10-3(e,f): Est. RR=1.49, p=0.001; Adj. RR=1.46, p=0.004; and Est. RR=1.54, p=0.005; Adj. RR=1.49, p=0.011, respectively). A marginally significant difference between Ranch Hands in the low plus high dioxin category and Comparisons was revealed in the adjusted analysis of skin neoplasms (Table 10-3(f): Adj. RR=1.25, p=0.073). Each contrast displayed more Ranch Hands than Comparisons with skin neoplasms. All other Model 3 contrasts were nonsignificant (Table 10-3(e,f): p>0.18).

The Model 4 unadjusted analysis revealed a significant inverse relation between skin neoplasms and 1987 dioxin levels (Table 10-3(g): Est. RR=0.88, p=0.012). After adjustment for covariates, the association was nonsignificant (Table 10-3(h): p=0.147).

10.2.2.1.2 Malignant Skin Neoplasms

The Model 1 enlisted flyer contrast revealed a marginally significantly higher percentage of a history of malignant skin neoplasms for Ranch Hands than for Comparisons in both the unadjusted and adjusted analyses (Table 10-4(a,b): Est. RR=1.79, p=0.059; Adj. RR=1.86, p=0.055, respectively). All other Model 1 contrasts were nonsignificant (Table 10-4(a,b): p>0.16).

Table 10-4. Analysis of Malignant Skin Neoplasms

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

Occupational Category	Group	n	Number (%) Yes	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***805***	***144 (17.9)***	***1.14 (0.90,1.45)***	***0.274***
	Comparison	***1,168***	***187 (16.0)***		
Officer	Ranch Hand	329	77 (23.4)	1.24 (0.88,1.74)	0.218
	Comparison	480	95 (19.8)		
Enlisted Flyer	Ranch Hand	140	29 (20.7)	1.79 (0.98,3.29)	0.059
	Comparison	173	22 (12.7)		
Enlisted Groundcrew	Ranch Hand	336	38 (11.3)	0.81 (0.53,1.24)	0.329
	Comparison	515	70 (13.6)		

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	***1.19 (0.93,1.54)***	***0.175***
Officer	1.29 (0.90,1.85)	0.161
Enlisted Flyer	1.86 (0.99,3.51)	0.055
Enlisted Groundcrew	0.86 (0.56,1.34)	0.509

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

Initial Dioxin Category Summary Statistics			Analysis Results for Log_2 (Initial Dioxin)[a]	
Initial Dioxin	n	Number (%) Yes	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	138	31 (22.5)	0.79 (0.64,0.96)	0.015
Medium	150	30 (20.0)		
High	151	18 (11.9)		

[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

n	Analysis Results for Log_2 (Initial Dioxin) Adjusted Relative Risk (95% C.I.)[a]	p-Value
439	0.87 (0.68,1.12)	0.287

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

Table 10-4. Analysis of Malignant Skin Neoplasms (Continued)

(e) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – UNADJUSTED				
Dioxin Category	n	Number (%) Yes	Est. Relative Risk (95% C.I.)[ab]	p-Value
Comparison	1,133	179 (15.8)		
Background RH	359	65 (18.1)	1.21 (0.88,1.66)	0.237
Low RH	210	47 (22.4)	1.52 (1.06,2.19)	0.023
High RH	229	32 (14.0)	0.84 (0.56,1.27)	0.417
Low plus High RH	439	79 (18.0)	1.12 (0.83,1.51)	0.457

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

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

(f) MODEL 3: RANCH HANDS AND COMPARISONS BY DIOXIN CATEGORY – ADJUSTED			
Dioxin Category	n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
Comparison	1,131		
Background RH	358	1.13 (0.81,1.58)	0.476
Low RH	210	1.45 (0.98,2.14)	0.062
High RH	229	1.19 (0.76,1.85)	0.453
Low plus High RH	439	1.30 (0.95,1.80)	0.104

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

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

(g) MODEL 4: RANCH HANDS – 1987 DIOXIN – UNADJUSTED				
1987 Dioxin Category Summary Statistics			Analysis Results for Log_2 (1987 Dioxin + 1)	
1987 Dioxin	n	Number (%) Yes	Estimated Relative Risk (95% C.I.)[a]	p-Value
Low	273	48 (17.6)	0.92 (0.81,1.04)	0.187
Medium	256	56 (21.9)		
High	269	40 (14.9)		

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

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