At the end of 15 years of surveillance, Ranch Hands as a group exhibited a nonsignificant increase in the risk of malignant neoplastic disease relative to Comparisons (relative risk=1.06, 95% confidence interval: [0.80,1.41]). Contrasts by military occupation were inconsistent and, therefore, not supportive of an adverse effect of herbicide or dioxin exposure on the occurrence of malignancies. Ranch Hand enlisted groundcrew, the occupation with the highest dioxin levels and, presumably, the highest herbicide exposure, exhibited a decreased prevalence (relative risk=0.78, 95% confidence interval: [0.51,1.19]). Enlisted flyers (relative risk=1.63, 95% confidence interval: [0.91,2.92]), and officers (relative risk=1.14, 95% confidence interval: [0.79,1.65]), occupations with lower dioxin levels, exhibited nonsignificant increases in the prevalence of malignant disease. The risk of malignant disease was not significantly increased among Ranch Hands having the highest dioxin levels (relative risk=1.01, 95% confidence interval: [0.66,1.57]). Longitudinal analyses found no significant group differences with regard to the risk of malignancy and no pattern suggestive of an adverse relation between herbicide or dioxin exposure and the occurrence of malignant neoplastic disease.

10.4 SUMMARY

Skin and systemic neoplasms, verified from a medical records review, and PSA were examined in the neoplasia assessment. Each health endpoint was examined for an association with exposure group (Model 1), initial dioxin (Model 2), categorized dioxin (Model 3), and 1987 dioxin levels (Model 4). Complete adjusted analyses were limited for many of the site-specific malignant systemic neoplasms because of the sparse number of neoplasms.

10.4.1 Model 1: Group Analysis

Several significant results were observed in the Model 1 adjusted analysis of the neoplasia endpoints. Each significant result showed more Ranch Hands than Comparisons with the specific skin or systemic type neoplasm; however, no significant results were found within the enlisted groundcrew stratum, the military occupational category believed to have been, on average, the most heavily exposed. Significantly more Ranch Hands than Comparisons had skin neoplasms (all types combined). This finding was true for officers and enlisted flyers, as well as all occupations combined. Ranch Hand enlisted flyers had a marginally significantly increase in malignant skin neoplasms in relation to Comparison enlisted flyers. An increase in benign skin neoplasms was observed in Ranch Hands over Comparisons, both when combining all occupations and when restricted to officers. Ranch Hand enlisted flyers exhibited an increase in basal cell carcinoma in relation to Comparison enlisted flyers. This result was primarily because of a marginally significant increase of basal cell carcinoma on the ear, face, head, or neck. Ranch Hand enlisted flyers showed an increase of nonmelanoma relative to Comparisons. This result also was primarily because of the increase in basal cell carcinoma in Ranch Hand enlisted flyers. Ranch Hands showed a marginally significant increase over Comparisons in malignant systemic neoplasms of the bronchus and lung and of the kidney and bladder. Complete results of the Model 1 analyses are shown in Table 10-40.

Table 10-40. Summary of Group Analysis (Model 1) for Neoplasia Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Medical Records				
Any Skin Neoplasm	+0.007	+0.034	+0.040	NS
Malignant Skin Neoplasm	NS	NS	NS*	ns
Benign Skin Neoplasm	+0.010	+0.031	NS	NS
Skin Neoplasm of Uncertain Behavior or Unspecified Nature	NS	ns	ns	NS
Any Basal Cell Carcinoma	NS	NS	NS*	ns
Basal Cell Carcinoma on Eye, Ear, Face, Head, and Neck	NS	NS	NS	ns
Basal Cell Carcinoma on Trunk	NS	NS	NS	ns
Basal Cell Carcinoma on Upper Extremities	ns	NS	ns	ns
Basal Cell Carcinoma on Lower Extremities	NS	NS	--	ns
Squamous Cell Carcinoma	NS	NS	NS	NS
Nonmelanoma	NS	NS	+0.042	ns
Melanoma	NS	NS	ns	NS
Any Systemic Neoplasm	NS	ns	NS	NS
Malignant Systemic Neoplasm	NS	NS	+0.049	NS
Benign Systemic Neoplasm	NS	ns	NS	NS
Systemic Neoplasm of Uncertain Behavior or Unspecified Nature	ns	NS	ns	ns
Malignant Systemic Neoplasm of Eye, Ear, Face, Head, and Neck	NS	NS	ns	ns
Malignant Systemic Neoplasm of Oral Cavity, Pharynx, and Larynx	ns	NS	ns	ns
Malignant Systemic Neoplasm of Thymus, Heart, and Mediastinum	NS	NS	--	NS
Malignant Systemic Neoplasm of Thyroid Gland	NS	NS	--	ns
Malignant Systemic Neoplasm of Bronchus and Lung	+0.008	NS	NS	NS
Malignant Systemic Neoplasm of Liver	NS	ns	NS	NS
Malignant Systemic Neoplasm of Colon and Rectum	NS	NS	NS	ns
Malignant Systemic Neoplasm of Kidney and Bladder	+0.046	NS	NS	NS
Malignant Systemic Neoplasm of Prostate	ns	ns	NS	ns
Malignant Systemic Neoplasm of Testicles	NS	NS	NS	NS
Malignant Systemic Neoplasm of Connective and Other Soft Tissues	ns	--	NS	ns
Hodgkin's Disease	ns	ns	--	ns
Non-Hodgkin's Lymphoma	ns	ns	--	NS

Table 10-40. Summary of Group Analysis (Model 1) for Neoplasia Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	UNADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	ns	ns	ns	NS
All Malignant Skin and Systemic Neoplasms	NS*	NS	+0.034	ns
All Skin and Systemic Neoplasms	+0.014	NS*	NS	NS
Laboratory				
Prostate-Specific Antigen (C)	ns	ns	NS	ns
Prostate-Specific Antigen (D)	NS	NS*	ns	ns

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

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

A capital "NS" denotes a relative risk of 1.00 or greater for discrete analysis or differences of means nonnegative for continuous analysis. A lowercase "ns" denotes a 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
Medical Records				
Any Skin Neoplasm	+0.005	+0.030	+0.040	NS
Malignant Skin Neoplasm	NS	NS	NS*	ns
Benign Skin Neoplasm	+0.011	+0.035	NS	NS
Skin Neoplasm of Uncertain Behavior or Unspecified Nature	NS	--	--	NS
Any Basal Cell Carcinoma	NS	NS	+0.046	ns
Basal Cell Carcinoma on Eye, Ear, Face, Head, and Neck	NS	NS	NS*	ns
Basal Cell Carcinoma on Trunk	NS	NS	NS	ns
Basal Cell Carcinoma on Upper Extremities	ns	ns	ns	ns
Basal Cell Carcinoma on Lower Extremities	NS	NS	--	ns
Squamous Cell Carcinoma	NS	NS	NS	NS
Nonmelanoma	NS	NS	+0.035	ns
Melanoma	NS	NS	--	NS
Any Systemic Neoplasm	ns	ns	ns	ns
Malignant Systemic Neoplasm	NS	NS	NS	ns
Benign Systemic Neoplasm	ns	ns	ns	NS
Systemic Neoplasm of Uncertain Behavior or Unspecified Nature	ns	ns	ns	ns

Table 10-40. Summary of Group Analysis (Model 1) for Neoplasia Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	ADJUSTED			
	All	Officer	Enlisted Flyer	Enlisted Groundcrew
Malignant Systemic Neoplasm of Eye, Ear, Face, Head, and Neck	ns	NS	ns	ns
Malignant Systemic Neoplasm of Oral Cavity, Pharynx, and Larynx	ns	NS	ns	ns
Malignant Systemic Neoplasm of Thymus, Heart, and Mediastinum	--	--	--	--
Malignant Systemic Neoplasm of Thyroid Gland	NS	NS	--	--
Malignant Systemic Neoplasm of Bronchus and Lung	NS*	NS	NS	--
Malignant Systemic Neoplasm of Liver	NS	--	--	NS
Malignant Systemic Neoplasm of Colon and Rectum	NS	NS	NS	ns
Malignant Systemic Neoplasm of Kidney and Bladder	NS*	NS	--	NS
Malignant Systemic Neoplasm of Prostate	ns	ns	NS	ns
Malignant Systemic Neoplasm of Testicles	--	--	--	--
Malignant Systemic Neoplasm of Connective and Other Soft Tissues	ns	--	--	--
Hodgkin's Disease	ns	ns	--	--
Non-Hodgkin's Lymphoma	ns	--	--	ns
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	ns	ns	--	NS
All Malignant Skin and Systemic Neoplasms	NS	NS	NS	ns
All Skin and Systemic Neoplasms	NS	NS	NS	ns
Laboratory				
Prostate-Specific Antigen (C)	NS	ns	NS	NS
Prostate-Specific Antigen (D)	NS	NS	ns	ns

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

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

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

10.4.2 Model 2: Initial Dioxin Analysis

The Model 1 group analysis showed significant Ranch Hand increases in the history of neoplasms relative to Comparisons. In contrast, analysis of the association of initial dioxin with neoplasms within Ranch Hands showed several significant results, but all dose-response relations were inverse in nature. As initial dioxin increased, the occurrence of a neoplasm decreased. Significant inverse dose-response related to skin neoplasms included all skin neoplasms, benign skin neoplasms, basal cell carcinoma, and basal cell carcinoma on the ear, face, head, and neck. The analysis of nonmelanoma was marginally significant.

The analysis of malignant systemic neoplasms of the thyroid gland was marginally significant, but this type of neoplasm decreased as initial dioxin increased. The prevalence of high PSA levels also decreased as initial dioxin increased. Results of all Model 2 analyses are shown in Table 10-41.

Table 10-41. Summary of Initial Dioxin Analysis (Model 2) for Neoplasia Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Medical Records		
Any Skin Neoplasm	–0.001	–0.028
Malignant Skin Neoplasm	–0.015	ns
Benign Skin Neoplasm	–0.022	–0.020
Skin Neoplasm of Uncertain Behavior or Unspecified Nature	ns	ns
Any Basal Cell Carcinoma	–<0.001	–0.014
Basal Cell Carcinoma on Eye, Ear, Face, Head, and Neck	–<0.001	–0.003
Basal Cell Carcinoma on Trunk	ns	NS
Basal Cell Carcinoma on Upper Extremities	–0.024	ns
Basal Cell Carcinoma on Lower Extremities	NS	NS
Squamous Cell Carcinoma	ns	ns
Nonmelanoma	–0.003	ns*
Melanoma	NS	NS
Any Systemic Neoplasm	ns	NS
Malignant Systemic Neoplasm	–0.001	ns
Benign Systemic Neoplasm	NS	ns
Systemic Neoplasm of Uncertain Behavior or Unspecified Nature	ns	NS
Malignant Systemic Neoplasm of Eye, Ear, Face, Head, and Neck	ns*	ns
Malignant Systemic Neoplasm of Oral Cavity, Pharynx, and Larynx	ns	NS
Malignant Systemic Neoplasm of Thymus, Heart, and Mediastinum	--	--
Malignant Systemic Neoplasm of Thyroid Gland	–0.046	ns*
Malignant Systemic Neoplasm of Bronchus and Lung	–0.030	ns
Malignant Systemic Neoplasm of Liver	NS	NS
Malignant Systemic Neoplasm of Colon and Rectum	ns	ns
Malignant Systemic Neoplasm of Kidney and Bladder	ns	NS

Table 10-41. Summary of Initial Dioxin Analysis (Model 2) for Neoplasia Variables (Ranch Hands Only) (Continued)

Variable	Unadjusted	Adjusted
Malignant Systemic Neoplasm of Prostate	–0.007	ns
Malignant Systemic Neoplasm of Testicles	ns	ns
Malignant Systemic Neoplasm of Connective and Other Soft Tissues	NS	NS
Hodgkin's Disease	--	--
Non-Hodgkin's Lymphoma	--	--
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	--	--
All Malignant Skin and Systemic Neoplasms	–0.001	ns
All Skin and Systemic Neoplasms	–0.017	ns
Laboratory		
Prostate-Specific Antigen (C)	–0.010	ns
Prostate-Specific Antigen (D)	–<0.001	–0.014

Notes: 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; slope negative for continuous analysis.
--: Analysis not performed because of the sparse number of Ranch Hands with an abnormality.

P-value given if p≤0.05.

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

10.4.3 Model 3: Categorized Dioxin Analysis

The unadjusted analysis of the skin neoplasia variables revealed several significant results. A significant increase of Ranch Hands in the background category relative to Comparisons was seen for all skin neoplasms combined and benign skin neoplasm. Only one contrast of Ranch Hands in the high dioxin category with Comparisons exhibited a marginally significant increase (neoplasm of the liver). Most significant results showed an increase in neoplasms of Ranch Hands in the low dioxin category relative to Comparisons. Significant or marginally significant increases of skin neoplasms in Ranch Hands in the low dioxin category were seen for all skin neoplasms, malignant skin neoplasms, basal cell carcinoma (primarily eye, ear, face, head, or neck) and nonmelanoma.

Similar to the skin neoplasm analyses, most results that were significant or marginally significant for the systemic neoplasm analyses were from the contrast of Ranch Hands in the low dioxin category with Comparisons. Any malignant systemic neoplasm, a malignant systemic neoplasm of bronchus and lung, a malignant systemic neoplasm of kidney and bladder, and a malignant systemic neoplasm of testicles were increased in Ranch Hands in the low dioxin category relative to Comparisons. In addition, an increase in all malignant skin and systemic neoplasms was observed for Ranch Hands in the low dioxin category. Complete results of the Model 3 analyses are shown in Table 10-42.

Table 10-42. Summary of Categorized Dioxin Analysis (Model 3) for Neoplasia Variables (Ranch Hands vs. Comparisons)

Variable	UNADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Medical Records				
Any Skin Neoplasm	+0.001	+0.005	ns	NS
Malignant Skin Neoplasm	NS	+0.023	ns	NS
Benign Skin Neoplasm	+<0.001	NS	ns	NS
Skin Neoplasm of Uncertain Behavior or Unspecified Nature	ns	NS	NS	NS
Any Basal Cell Carcinoma	NS	+0.012	ns	NS
Basal Cell Carcinoma on Eye, Ear, Face, Head, and Neck	NS	+0.020	ns	NS
Basal Cell Carcinoma on Trunk	NS	NS	ns	NS
Basal Cell Carcinoma on Upper Extremities	ns	NS	ns	ns
Basal Cell Carcinoma on Lower Extremities	NS	NS	ns	ns
Squamous Cell Carcinoma	NS	NS	ns	NS
Nonmelanoma	NS	+0.034	ns	NS
Melanoma	NS	NS	NS	NS
Any Systemic Neoplasm	ns	NS*	NS	NS
Malignant Systemic Neoplasm	ns	+<0.001	ns	NS
Benign Systemic Neoplasm	NS	NS	NS	NS
Systemic Neoplasm of Uncertain Behavior or Unspecified Nature	NS	NS	ns	ns
Malignant Systemic Neoplasm of Eye, Ear, Face, Head, and Neck	ns	NS	ns	NS
Malignant Systemic Neoplasm of Oral Cavity, Pharynx, and Larynx	ns	NS	ns	NS
Malignant Systemic Neoplasm of Thymus, Heart, and Mediastinum	NS*	--	--	--
Malignant Systemic Neoplasm of Thyroid Gland	ns	NS*	ns	NS
Malignant Systemic Neoplasm of Bronchus and Lung	NS	+<0.001	ns	+0.003
Malignant Systemic Neoplasm of Liver	ns	ns	NS*	NS
Malignant Systemic Neoplasm of Colon and Rectum	ns	NS*	ns	NS
Malignant Systemic Neoplasm of Kidney and Bladder	NS	+0.015	NS	NS*
Malignant Systemic Neoplasm of Prostate	ns	NS	ns	ns
Malignant Systemic Neoplasm of Testicles	--	+0.024	NS	+0.034
Malignant Systemic Neoplasm of Connective and Other Soft Tissues	ns	ns	NS	NS
Hodgkin's Disease	ns	ns	ns	ns
Non-Hodgkin's Lymphoma	ns	ns	ns	ns

Table 10-42. Summary of Categorized Dioxin Analysis (Model 3) for Neoplasia Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	UNADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	NS	ns	ns	ns
All Malignant Skin and Systemic Neoplasms	NS	+<0.001	ns	NS
All Skin and Systemic Neoplasms	+0.030	+0.007	NS	NS*
Laboratory				
Prostate-Specific Antigen (C)	ns	NS	ns*	ns
Prostate-Specific Antigen (D)	ns	+0.040	ns	NS

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

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

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

Variable	ADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Medical Records				
Any Skin Neoplasm	+0.004	+0.011	NS	NS*
Malignant Skin Neoplasm	NS	NS*	NS	NS
Benign Skin Neoplasm	+0.001	NS	ns	NS
Skin Neoplasm of Uncertain Behavior or Unspecified Nature	ns	NS	ns	NS
Any Basal Cell Carcinoma	NS	+0.026	ns	NS
Basal Cell Carcinoma on Eye, Ear, Face, Head, and Neck	NS	NS*	ns	NS
Basal Cell Carcinoma on Trunk	ns	NS	NS	NS
Basal Cell Carcinoma on Upper Extremities	ns	ns	ns	ns
Basal Cell Carcinoma on Lower Extremities	NS	ns	NS	ns
Squamous Cell Carcinoma	NS	NS	NS	NS
Nonmelanoma	NS	NS*	NS	NS
Melanoma	NS	NS	NS	NS*
Any Systemic Neoplasm	ns*	ns	ns	ns
Malignant Systemic Neoplasm	ns	+0.012	ns	NS
Benign Systemic Neoplasm	ns	ns	NS	ns
Systemic Neoplasm of Uncertain Behavior or Unspecified Nature	ns	ns	ns	ns

Table 10-42. Summary of Categorized Dioxin Analysis (Model 3) for Neoplasia Variables (Ranch Hands vs. Comparisons) (Continued)

Variable	ADJUSTED			
	Background Ranch Hands vs. Comparisons	Low Ranch Hands vs. Comparisons	High Ranch Hands vs. Comparisons	Low plus High Ranch Hands vs. Comparisons
Malignant Systemic Neoplasm of Eye, Ear, Face, Head, and Neck	ns	NS	ns	ns
Malignant Systemic Neoplasm of Oral Cavity, Pharynx, and Larynx	ns	NS	ns	ns
Malignant Systemic Neoplasm of Thymus, Heart, and Mediastinum	--	--	--	--
Malignant Systemic Neoplasm of Thyroid Gland	--	NS	--	--
Malignant Systemic Neoplasm of Bronchus and Lung	NS	+0.008	--	--
Malignant Systemic Neoplasm of Liver	--	--	NS*	--
Malignant Systemic Neoplasm of Colon and Rectum	ns	NS	ns	NS
Malignant Systemic Neoplasm of Kidney and Bladder	NS	+0.044	NS	NS*
Malignant Systemic Neoplasm of Prostate	ns*	ns	ns	ns
Malignant Systemic Neoplasm of Testicles	--	--	--	--
Malignant Systemic Neoplasm of Connective and Other Soft Tissues	--	--	NS	--
Hodgkin's Disease	ns	--	--	--
Non-Hodgkin's Lymphoma	ns	--	--	--
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	NS	--	--	--
All Malignant Skin and Systemic Neoplasms	ns	+0.035	NS	NS
All Skin and Systemic Neoplasms	NS	NS	ns	NS
Laboratory				
Prostate-Specific Antigen (C)	ns	NS	NS	NS
Prostate-Specific Antigen (D)	ns	NS	NS	NS

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

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

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

10.4.4 Model 4: 1987 Dioxin Analysis

Results from the adjusted 1987 dioxin analysis of neoplasms showed few significant results. As 1987 dioxin increased, significant increases in basal cell carcinoma on the trunk and a malignant neoplasm of the liver were found. Significant decreases with increasing levels of 1987 dioxin were found for benign skin neoplasms and a malignant neoplasm of the thymus, heart, or mediastinum. Other results that were significant in the unadjusted analysis were nonsignificant after adjustment for covariates. Results of all analyses of 1987 dioxin are provided in Table 10-43.

Table 10-43. Summary of 1987 Dioxin Analysis (Model 4) for Neoplasia Variables (Ranch Hands Only)

Variable	Unadjusted	Adjusted
Medical Records		
Any Skin Neoplasm	–0.012	ns
Malignant Skin Neoplasm	ns	NS
Benign Skin Neoplasm	–0.003	–0.005
Skin Neoplasm of Uncertain Behavior or Unspecified Nature	NS	NS
Any Basal Cell Carcinoma	–0.037	ns
Basal Cell Carcinoma on Eye, Ear, Face, Head, and Neck	–0.021	ns
Basal Cell Carcinoma on Trunk	ns	+0.016
Basal Cell Carcinoma on Upper Extremities	ns	NS
Basal Cell Carcinoma on Lower Extremities	ns	ns
Squamous Cell Carcinoma	ns	NS
Nonmelanoma	ns*	NS
Melanoma	NS	NS
Any Systemic Neoplasm	NS	NS
Malignant Systemic Neoplasm	ns	NS
Benign Systemic Neoplasm	NS	NS
Systemic Neoplasm of Uncertain Behavior or Unspecified Nature	ns	NS
Malignant Systemic Neoplasm of Eye, Ear, Face, Head, and Neck	ns	NS
Malignant Systemic Neoplasm of Oral Cavity, Pharynx, and Larynx	NS	NS
Malignant Systemic Neoplasm of Thymus, Heart, and Mediastinum	–0.038	–0.017
Malignant Systemic Neoplasm of Thyroid Gland	ns	ns
Malignant Systemic Neoplasm of Bronchus and Lung	ns	NS
Malignant Systemic Neoplasm of Liver	NS*	+0.042
Malignant Systemic Neoplasm of Colon and Rectum	NS	NS
Malignant Systemic Neoplasm of Kidney and Bladder	NS	NS
Malignant Systemic Neoplasm of Prostate	ns	ns
Malignant Systemic Neoplasm of Testicles	NS	NS
Malignant Systemic Neoplasm of Connective and Other Soft Tissues	NS	NS
Hodgkin's Disease	ns	ns

Table 10-43. Summary of 1987 Dioxin Analysis (Model 4) for Neoplasia Variables (Ranch Hands Only) (Continued)

Variable	Unadjusted	Adjusted
Non-Hodgkin's Lymphoma	ns	ns
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	ns	ns
All Malignant Skin and Systemic Neoplasms	ns	NS
All Skin and Systemic Neoplasms	ns	ns
Laboratory		
Prostate-Specific Antigen (C)	–0.043	ns
Prostate-Specific Antigen (D)	ns	NS

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

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

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

10.5 CONCLUSION

Several analyses showed significantly more Ranch Hands than Comparisons with a history of malignant skin or systemic neoplasms; however, no significant results were found within the enlisted groundcrew stratum, the military occupational category believed to have been, on average, the most heavily exposed. When the association between initial dioxin and malignant neoplasms was examined within Ranch Hands, the neoplasm occurrence decreased as initial dioxin increased. A significant increase of malignant neoplasms for Ranch Hands in the low dioxin category relative to Comparisons was observed, but there was no such increase in Ranch Hands in the high dioxin category. In summary, at the end of 15 years of surveillance, Ranch Hands do not exhibit a significantly increased risk for neoplastic disease, nor do they show a positive dose-response relation between dioxin and malignant neoplastic conditions.

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11 NEUROLOGICAL ASSESSMENT

11.1 INTRODUCTION

11.1.1 Background

The recent association of neurological symptoms with herbicide exposure has motivated much of the research toward the potential neurotoxicity of dioxin. Studies of industrial accidents, as discussed subsequently in this section, have demonstrated that the mixed sensorimotor neuropathy associated with extreme chlorophenol toxicity is reversible and that there is little scientific evidence to date for any chronic central or peripheral neurological disease in humans associated with low-level 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) exposure. Neurobehavioral endpoints in humans, the subject of intensive investigation in this and other studies of Vietnam veterans, are considered separately in Chapter 12, Psychological Assessment.

Much of the basic research in animal models has focused on neurobehavioral sequelae consequent to dichlorophenoxyacetic acid (2,4-D, a component of Agent Orange) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) rather than dioxin toxicity in laboratory animal experiments (1–4). In another series of studies, the neurobehavioral effects of exposure to an ester of 2,4-D were found to be rapidly reversible, and the authors proposed a cellular rather than biochemical basis for the tolerance that developed with repeated injections (5, 6).

Several studies have investigated the neurotoxic effects of dioxin in laboratory animals with inconsistent results. Rats given a high dose of dioxin (1,000 μg/kg) intraperitoneally demonstrated no apparent neurological deficits (7). The intracerebroventricular administration of dioxin proved far more toxic than the subcutaneous route in producing a wasting syndrome in rats, although specific neurological indices were not examined (8). In another study, the neuromuscular effects associated with acute lethal doses of dioxin in rats were primarily in muscle tissue rather than peripheral nerves (9).

Two experimental animal studies can be cited as more relevant to the question of dioxin-induced neurotoxicity in humans. In the first study (10), strengthened by the inclusion of electrophysiologic measurements, Wistar rats received a single intraperitoneal low dose of dioxin in one of four strengths. Electrophysiologic studies of the sciatic nerve after injection documented dose-dependent and statistically significant reductions in motor and sensory nerve conduction velocities relative to the controls. In a companion report, the same authors provide histopathologic correlations with electrophysiologic findings (11). Ten months after exposure, microscopic studies confirmed the histologic appearance of a severe peripheral neuropathy of the axonal and demyelinating type.

In humans, there is only circumstantial evidence linking 2,4-D exposure to neurotoxicity, and the arguments against a causal relation have been summarized in a review article (12). Toxic doses of 2,4-D, as much as 3,600 mg given intravenously in a single dose to a human and a cumulative dose of 16,312 mg administered over 5 weeks, induced transient neurological signs and symptoms but no long-term sequelae (13).

A host of neurological symptoms has been reported following dioxin exposure and has been grouped under the generic term of "neurasthenia." Numerous studies have been published describing neurological sequelae in populations exposed to dioxin by occupation (14–21), environmental contamination (22–26)

and industrial accidents (27–33), and in association with service in Southeast Asia (SEA) during the Vietnam War (34–40).

The 1976 chemical explosion in Seveso, Italy, has provided a basis for numerous reports on the exposed population (27–30, 32, 33), and several of these reports have included clinical and laboratory indices in the examination protocols, most of which have focused on signs and symptoms of peripheral neuropathy as primary clinical endpoints. In one study, 152 subjects with chloracne, a marker for high-level dioxin exposure, were compared with controls. An abnormality was found in only 1 of 13 neurophysiologic indices, and none of the exposed subjects were found to have a peripheral neuropathy by World Health Organization criteria (30). Other investigators who included electromyographic studies in the examination protocols reached similar conclusions (27, 29, 32), as did those studying the populations exposed consequent to uncontrolled chemical reactions that occurred in Germany in 1953 (31) and in Nitro, West Virginia, in 1949 (17).

In contrast, one occupational study of 47 railroad workers examined 6 years after a chemical spill revealed evidence, through electrophysiologic measurements, for a peripheral neuropathy in 43 of these workers. High prevalences of dystonia (53%) and tremor (78%) were documented (14). These results have not been confirmed by any other studies, and the conclusions were limited by the lack of a control group and by exposure to other chemicals.

Point-source environmental exposure to dioxin has been the focus of numerous epidemiological studies, some of which have included neurological indices in their protocols (22–26). In 1971, waste byproducts contaminated with dioxin were mixed with oils and widely sprayed for dust control in residential areas in eastern Missouri. Soil concentrations in some areas reached 2,200 parts per billion, far exceeding the highest degree of ground contamination that occurred at Seveso. Comprehensive medical evaluations of exposed and unexposed cohorts included detailed neurological examinations and, in one report (24), quantitative studies of tactile, vibratory, and thermal sensory perception. The Missouri dioxin studies have been summarized in a review article (26) and, to date, none has found any clinical evidence for central or peripheral neurological disease associated with exposure to dioxin. In the only Missouri study to relate neurological endpoints to tissue levels of dioxin (23), no associations were found between the body burden of dioxin and abnormalities in deep tendon reflexes or pain and vibratory sensation.

An epidemiological study conducted by the National Institute of Occupational Safety and Health is one of few to relate serum dioxin levels to neurological indices (20). The prevalence of peripheral neuropathy was determined in 265 workers with a mean serum dioxin level of 220 parts per trillion (ppt) 15 years after exposure and in 244 referents with a level of 7 ppt. The diagnosis of peripheral neuropathy was established by symptoms and by data collected during physical examination, electrophysiologic studies, and quantitative sensory testing. Although the study could not rule out neurological symptoms associated with acute exposure, there was no evidence for a dose-response relation between dioxin levels and peripheral neuropathy.

Few studies of Vietnam veterans have incorporated neurological data into their protocols and, with the exception of the Air Force Health Study (AFHS), none has correlated neurological indices with tissue levels of dioxin. One large-scale study of American Legion veterans who served in Vietnam found an increased incidence of reported neurobehavioral disorders among veterans who reported exposure to herbicides (34).

The Vietnam Experience Study, conducted by the United States Centers for Disease Control and Prevention, compared the health status of 2,490 Vietnam veterans with 1,972 non-Vietnam veterans (35). The study protocol included comprehensive neurological examinations, nerve conduction velocity

studies, and neurophysiologic indices of vibratory, thermal, and auditory sensation. Aside from an increased prevalence of combat-related high frequency hearing loss in a pattern consistent with prior noise exposure, no neurological abnormalities were noted in association with service in Vietnam.

In the baseline examination of the AFHS (36), an increased prevalence of abnormal Babinski reflexes was noted in Ranch Hand personnel relative to Comparisons, a finding not confirmed at the 1985 (37), 1987 (38), or 1992 (39) follow-up examinations. In the 1987 examination, Ranch Hand participants were found to have more coordination abnormalities than Comparisons, but subsequent analyses found no correlation with serum dioxin levels. A few statistically significant associations were noted but not in a pattern consistent with a dose-response effect (40). In the AFHS 1992 examination, the prevalence of neurological disease was comparable in the Ranch Hand and Comparison groups, and there was no consistent evidence for a dose-response effect with either estimated initial dioxin levels or current dioxin levels (39). In the most recent report published by the Institute of Medicine (41), the committee concluded that there is "limited/suggestive" evidence of an association between exposure to certain herbicides used in Vietnam and the development of an acute or subacute transient peripheral neuropathy.

In summary, the animal research and human epidemiological studies cited above suggest that the peripheral nervous system is a target organ for acute dioxin toxicity. Longitudinal studies suggest that the neurological signs and symptoms attributable to heavy acute exposure resolve over time and are not associated with any long-term sequelae. Exposures equivalent to those likely to have been encountered by Vietnam veterans have not been associated with persistent neurological abnormalities.

11.1.2 Summary of Previous Analyses of the Air Force Health Study

11.1.2.1 1982 Baseline Study Summary Results

The 1982 AFHS neurological assessment consisted of questionnaire, physical examination, and electromyographic data obtained by examiners and technicians who were blind to the group identity of each participant. The physical examination required an average of 30 minutes to complete. Analyses were adjusted for reported alcohol usage, exposure to insecticides and industrial chemicals, and glucose intolerance (diabetes).

Results of the questionnaire disclosed no significant group differences in reported neurological diseases. The physical examination did not reveal any statistically significant group differences in the function of the 12 cranial nerves. Peripheral nerve function was assessed by the quality of four reflexes (patellar, Achilles, biceps, and Babinski); muscle strength or bulk; and reaction to the stimuli of pinprick, light touch, and vibration. Other than a statistically significant increase ($p=0.03$) in Ranch Hand Babinski reflexes, significant group differences were not detected.

Nerve conduction velocities were obtained on the ulnar nerve above and below the elbow and the peroneal nerve. The results for each segmental measurement were nearly identical in the Ranch Hand and Comparison groups. Conduction velocity showed highly significant inverse relations to both alcohol and diabetes in almost all of the anatomic measurements. No group associations or interactions were detected with the reported exposure to industrial and degreasing chemicals and insecticides.

No significant group differences were detected in four measures of central neurological function (tremor, finger-nose coordination, modified positive Romberg sign, or abnormal gait). Alcohol usage was significantly associated with the presence of tremor, and glucose intolerance was highly correlated to abnormal balance and the presence of tremor.

11.1.2.2 1985 Follow-up Study Summary Results

The 1985 AFHS neurological examination did not include the measurements of nerve conduction velocities, but otherwise repeated the baseline examination protocol. The questionnaire maintained a historical focus on neurasthenia through five questions for the 1982-1985 interval. With this similarity in examination and questionnaire, the dependent variables of the analyses were the same as those of the baseline study.

Interval questionnaire data (1982–1985) on neurological illness, verified by medical records, revealed no significant group differences. These data were added to verified baseline examination historical information to assess possible differences in the lifetime experience of neurological disease. Again, there was no significant difference between the Ranch Hand and Comparison groups.

The neurological examination evaluated neurological integrity in three broad areas: cranial nerve function, peripheral nerve status, and central nervous system (CNS) coordination. Assessment of the 12 cranial nerves was based on the measurement of 15 variables. Two summary indices were constructed. Neither the unadjusted nor the adjusted analyses disclosed any statistically significant group differences, although two variables (speech and tongue position) were of marginal significance, with Ranch Hands faring worse than Comparisons. One of the two cranial nerve summary indices was marginally significant, again with the Ranch Hands adversely affected. In contrast to the baseline examination, there was no significant group difference in Babinski reflex. The unadjusted and adjusted analyses of peripheral nerve function, as measured by eight variables (four reflexes, three sensory determinations, and muscle mass), did not reveal significant group differences. Coordination was evaluated by four measurements and a constructed summary variable. Hand tremor was found to be of marginal significance, with Ranch Hands faring slightly worse than Comparisons. The CNS summary index showed significant adverse effects for Ranch Hands.

In a longitudinal analysis of the Romberg sign and the Babinski reflex, only the Babinski reflex revealed a significant difference between the baseline examination and the 1985 follow-up examination, with the Ranch Hands shifting from significant adverse findings at the baseline examination to nonsignificant findings at the 1985 follow-up examination.

Overall, the 1985 follow-up examination findings were similar to the baseline examination findings; however, several distinct patterns were evident from the analyses:

- Substantially fewer abnormalities were detected at the 1985 follow-up examination than at the baseline examination for almost all of the variables.
- The decrease in abnormalities was similar in both groups.
- The adjusted analyses were uniformly similar to the unadjusted analyses.
- A significant result was found for the constructed CNS summary variable, and a marginally significant result was found for the constructed cranial nerve index excluding range of motion, both in the adverse direction.
- Although statistical significance at the pre-assigned significance level of 0.05 was not achieved for any of the measurement variables, the Ranch Hand group tended to have a greater percentage of abnormalities.

In conclusion, none of the 27 neurological variables demonstrated a significant group difference, although several showed an aggregation of abnormalities in the Ranch Hand group, which emphasized the need for continued surveillance. Historical reporting of neurological disease was similar in both

groups. The longitudinal analyses disclosed a reversal of significant increase in Babinski reflex abnormalities at the baseline examination to nonsignificant difference (RR=1.02) at the 1985 follow-up examination for the Ranch Hands.

11.1.2.3 1987 Follow-up Study Summary Results

The neurological health of the Ranch Hand group was not substantially different from the Comparison group. For the questionnaire variables related to neurological disease, Ranch Hands had significantly more hereditary and degenerative diseases, such as benign essential tremor. The statistical results of the group contrasts for 30 physical examination variables relating to cranial nerve function, peripheral nerve status, and CNS coordination processes generally were not significant. Unadjusted analyses disclosed marginally significantly more balance (Romberg sign) and coordination abnormalities for Ranch Hands than for Comparisons. Conversely, Ranch Hands had significantly fewer biceps reflex abnormalities than Comparisons. The longitudinal analyses for the cranial nerve index and the CNS index revealed no significant differences.

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

Overall, the neurological assessment did not indicate that dioxin was associated with neurological disease, although some analyses revealed a significant association between dioxin levels and CNS index and coordination. The adjusted analyses for the historical questionnaire variables were not significant and few statistically significant results were noted for the physical examination variables. The group contrast from the 1987 follow-up examination found that Ranch Hands had significantly more hereditary and degenerative diseases (mostly benign essential tremor) than Comparisons, but the serum dioxin analyses provided no support for the hypothesis that dioxin levels were associated with an increased risk of these diseases. The adjusted categorized current dioxin analyses for coordination found that the relative risk was significantly greater than 1.0 for Ranch Hands in the high current dioxin category. This was consistent with the previous analysis of the 1987 follow-up data, where the Ranch Hand group had significantly more coordination abnormalities than the Comparison group (1.5 percent versus 0.6 percent). The serum dioxin analyses showed significant adverse associations with the CNS index, including a marginally significant association with initial dioxin in the longitudinal analyses.

11.1.2.5 1992 Follow-up Study Summary Results

Overall, the neurological assessment found the prevalence of neurological disease to be comparable between the Ranch Hand and Comparison groups, and showed no consistent evidence of a dose-response effect with either estimated initial dioxin levels or current dioxin levels. In the group contrasts stratified by occupation, Ranch Hand enlisted groundcrew had significantly more cranial nerve index abnormalities than Comparison enlisted groundcrew. The enlisted groundcrew was the military occupation category with the highest average levels of dioxin; however, analyses of serum dioxin levels did not exhibit a dose-response trend.

11.1.3 Parameters for the 1997 Neurological Assessment

11.1.3.1 Dependent Variables

The neurological assessment was based on extensive physical examination data on cranial nerve function, peripheral nerve status, and CNS coordination processes. This information was supplemented by verified histories of neurological diseases. Participants with a positive serological test for syphilis and

participants who tested positive for the human immunodeficiency virus (HIV) were excluded from the analysis of all dependent variables.

11.1.3.1.1 Medical Records Variables

The 1997 questionnaire captured data on the occurrence of neurological disorders. Positive responses were verified by a medical records review and combined with information from the baseline examination and the 1985, 1987, and 1992 follow-up examinations. The neurological diseases and disorders were classified into four categories of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) manual: inflammatory diseases (ICD-9-CM codes 320.0–326), hereditary and degenerative diseases (ICD-9-CM codes 330.0–337.9), peripheral disorders (ICD-9-CM codes 350.1–359.9), and other neurological disorders (ICD-9-CM codes 340–349.9). The neurological inflammatory diseases found in this study consisted of meningitis caused by bacterial infection, meningitis of unknown cause, and encephalitis of unknown cause. The majority of other neurological disorders were unspecified encephalopathies, but conditions such as multiple sclerosis, other demyelinating diseases of the CNS, hemiplegia, other paralytic syndromes, epilepsy, migraine, catalepsy or narcolepsy, other conditions of the brain, and other unspecified disorders of the CNS were included. Each of the four disorders was coded as "yes" or "no."

Participants with a verified pre-SEA history of the disorder were excluded from all analyses pertaining to that disorder.

11.1.3.1.2 Physical Examination Data

11.1.3.1.2.1 Cranial Nerve Function

The evaluation of cranial nerve function was based on the following 15 variables: smell, visual fields, light reaction, ocular movement, facial sensation, corneal reflex, jaw clench, smile, palpebral fissure, balance, gag reflex, speech, tongue position relative to midline, palate and uvula movement, and neck movement. All of these variables were scored as "normal" or "abnormal," except for jaw clench and palate and uvula movement, which were scored as "symmetric" or "deviated." For variables with left and right determinations, the two results were combined to produce a single normal or abnormal result, where normal indicated that both responses were normal, and abnormal indicated that at least one of the responses was abnormal. Abnormal speech conditions included aphasia, dysarthria, agnosia, and other speech abnormalities. Neck range of motion was coded as abnormal if there was a decreased range of motion forward or backward or to the left or right. Neck movement was evaluated by a shoulder shrug and by applying manual resistance to the cheeks to evaluate the strength of lateral rotation. No abnormal neck movements were found at the 1997 examination.

A cranial nerve index was created by combining responses for the 15 cranial nerve parameters. This index was classified as abnormal if at least one of the determinations was abnormal and was classified as normal if all of the cranial nerve parameters were normal.

11.1.3.1.2.2 Musculoskeletal and Vertebral Column Function

The examining neurologist asked each participant to move his head to the left and right, and to tilt his head forward and backward. This test assessed the musculoskeletal and vertebral column function. This neck range of motion variable was coded as abnormal if there was a decreased range of motion forward or backward or to the left or right.

11.1.3.1.2.3 Peripheral Nerve Status

Peripheral nerve status was assessed by light pinprick, light touch (cotton sticks), visual inspection of muscle mass (and palpation, if indicated), three deep tendon reflexes (patellar, Achilles, and biceps), and the Babinski reflex. In addition, four indices to assess bilateral symmetric distal sensory or sensorimotor polyneuropathy were analyzed. These indices were constructed based on testing of ankle and toe flexors, coordination, deep tendon reflexes, light touch, pinprick, vibration at the ankle, toe position, and a vibrotactile measurement of both great toes.

A vibrotactile measurement of both the left and right great toes was performed as part of a collaborative effort with the National Institute of Dental Research. A Vibratron II® device was used to measure vibrotactile threshold on both the left and right great toes. The Vibratron II® provided a noninvasive means of measuring the sensitivity to vibration of a participant's feet. Following instructions from the manufacturer, the Vibratron II® was calibrated prior to the start of the physical examinations and at the midpoint of the examination period. Participants whose great toes could be examined but who sensed no vibration were included in the analysis at a level equal to the highest recorded measurement (22.8 vibrational units [VU]) to represent an extreme loss of sensitivity to vibration. The Vibratron II® device recorded measurements in vibrational units. A transformation was used to convert the vibrational units to a standardized unit, such as microns of displacement, to facilitate comparison with other studies. The formula used in this study, as determined by the manufacturer, was

$$\text{Displacement (microns)} = 0.5 \bullet VU^2.$$

The instrument was calibrated prior to and once (at the midpoint) during the study period. The displacement measurements were transformed to the natural logarithm scale to enhance normal distribution assumptions for analysis. The left and right great toes were analyzed separately. For each great toe, the average (in log microns) of four of seven trials was determined. The four trials were those remaining after eliminating the results of the first of the seven trials and the high and low readings of the other six results following a method of limits protocol (42). The average was calculated for each participant who had four nonzero measurements, after eliminating the results of the first of the seven trials and the high and low readings of the other six results.

Pinprick and light touch were considered normal if the reaction was normal on both legs. A variable to judge muscle status was constructed using data on bulk; tone of upper and lower extremities; and the strength of distal wrist extensors, ankle and toe flexors, proximal deltoids, and hip flexors. Bulk was classified as either "normal" or "abnormal"; tone was classified as "abnormal" if there was either a decreased or increased response on either the left side, right side, or both sides. The strength of distal wrist extensors, ankle and toe flexors, proximal deltoids, and hip flexors was considered "abnormal" if either or both the left or right side was decreased. Composite muscle status was classified as "normal" if all of the components were normal on both the left and right sides and "abnormal" if at least one of the components was abnormal on either or both sides. The patellar, Achilles, and biceps reflexes were coded as "normal" if they were sluggish, active, or very active and were classified as "abnormal" if absent.

Three indices to assess polyneuropathy were based on a severity index. The endpoints discussed previously in this section assessed unilateral abnormalities, whereas these indices assessed bilateral abnormalities. These indices were considered abnormal only if both the left and right determinations were abnormal. These indices were based on the following seven conditions or sets of conditions:

- Both left and right ankle and toe flexors were abnormal (no=0, yes=1)

- The Romberg sign (equilibratory) was abnormal (no=0, yes=1)
- Both left and right Achilles reflexes were absent (no=0, yes=1)
- Reaction to a light touch was abnormal on both the left and right legs (no=0, yes=1)
- Reaction to a pinprick was abnormal on both the left and right legs (no=0, yes=1)
- Both left and right ankle vibrations were abnormal (no=0, yes=1)
- The position of both the left and right great toe was abnormal (no=0, yes=1).

A polyneuropathy severity index, which ranged from 0 to 7, was constructed as the sum of the above seven scores. The polyneuropathy severity index was classified as "mild" (index = 0, 1, or 2), "moderate" (index = 3 or 4), or "severe" (index = 5, 6, or 7). A second index, termed a polyneuropathy prevalence indicator, was coded as "abnormal" if the polyneuropathy severity index was at least 1 and "normal" if the polyneuropathy severity index was 0. A third index, termed a multiple polyneuropathy index, was coded as "abnormal" if the polyneuropathy severity index was at least 2 and "normal" if the polyneuropathy severity index was 0 or 1.

In addition, a confirmed polyneuropathy index was constructed as follows:

If at least two of the following three conditions hold,

- Both left and right Achilles reflexes were absent
- Reaction to a pinprick was abnormal on both the left and right legs
- Both left and right ankle vibrations were abnormal

and the minimum of the left and right toe averages (in log microns) was greater than 4.02, the confirmed polyneuropathy index was coded as "abnormal." If the minimum vibrotactile measurement was less than or equal to 4.02, or no more than one of the above conditions was present, the confirmed polyneuropathy index was coded as "normal." The value of 4.02 was determined by taking the minimum value of the left and right great toe average for each participant and using the 90^{th} percentile of the minimum values for Comparisons.

Participants with peripheral edema in the lower extremities were excluded from the analyses of pinprick and light touch. The analysis of the Achilles reflex excluded participants with a transient or sustained clonus in this reflex. The analysis of the patellar reflex excluded participants with a transient or sustained clonus in this reflex. Participants with peripheral edema of the lower extremities and participants with transient clonus or sustained clonus results for the Achilles reflex were excluded from the analysis of polyneuropathy indices, because pinprick, light touch, and the Achilles reflex were a component of each of the polyneuropathy indices.

11.1.3.1.2.4 CNS Coordination Processes

The evaluation of CNS coordination processes was based on the analysis of the following variables: tremor, coordination, Romberg sign, gait, and a CNS index. For these variables, multiple determinations, which include left and right as well as upper and lower responses, were combined to form a single result. A result was classified as "normal" if all determinations were normal and "abnormal" if at least one determination was abnormal. Tremor was examined for the left and right upper and lower extremities. Abnormal tremors included resting, essential, intention, and "other tremors." Coordination was a composite index defined as "normal" if the Romberg sign, finger-nose-finger and heel-knee-shin coordination processes, rapidly alternating movements of pronation and supination of hands, and rapid

patting were normal. The Romberg sign variable is equivalent to the "balance" variable analyzed as part of the cranial nerve function assessment. The gait variable was based on the examining physician's assessment of the participant's gait. An abnormal gait included conditions such as broad-based, small-stepped, ataxic, or other irregular gait patterns. A CNS index was constructed and was a composite variable based on tremor, coordination, and gait. This index was coded as "normal" if all three of the components were normal and abnormal otherwise.

11.1.3.2 Covariates

Age, race, military occupation, lifetime alcohol history, reported exposure to insecticides, reported exposure to industrial chemicals, reported exposure to degreasing chemicals, and diabetic class were covariates for all adjusted statistical analyses.

Age, race, and military occupation were determined from military records. Lifetime alcohol history was based on self-reported information from the 1997 questionnaire and combined with similar information gathered at the 1987 and 1992 follow-ups. The participants' lifetime exposures through 1992 to insecticides, industrial chemicals, and degreasing chemicals were updated with information reported in the 1997 questionnaire.

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.

In the 1997 questionnaire, a general screening question on diabetes was posed. Each participant was asked during the in-person health interview the following question: "Since the date of the last interview, has a doctor told you for the first time that you had diabetes?" All affirmative responses were verified by a medical records review and added to previously reported and verified information on diabetes from the 1982 baseline examination and the 1985, 1987, and 1992 follow-up examinations for each participant. Participants with a verified history of diabetes were combined with those participants with a 2-hour postprandial glucose level of 200 mg/dl or greater at the 1997 physical examination and classified as "diabetic" for the diabetic class covariate. Those participants without a verified history of diabetes and with a 2-hour postprandial glucose level of less than 200 mg/dl at the 1997 physical examination were classified as either "impaired" (140 mg/dl <2-hour postprandial glucose < 200 mg/dl) or "normal" (2-hour postprandial glucose <140 mg/dl).

Two additional covariates based on self-reported information were used for the confirmed polyneuropathy indicator dependent variable. The 1997 questionnaire asked each study participant whether he had worked for 30 days or more with lead, mercury, chromium, nickel, copper, cadmium, manganese, arsenic, selenium, or molybdenum. Responses were combined to form a composite exposure to heavy metals covariate. The participant also was asked in the 1997 questionnaire whether he had ever worked for 30 days or more with vibrating power equipment or tools. The response (yes or no) to this question also was used as a covariate in the assessment of the confirmed polyneuropathy indicator dependent variable.

11.1.4 Statistical Methods

Table 11-1 summarizes the statistical analyses performed for the neurological assessment. The first part of Table 11-1 lists the dependent variables analyzed, data source, data form, cutpoints, covariates, and statistical methods. The second part of this table provides a further description of covariates examined. A covariate was used in its continuous form whenever possible for adjusted analyses; 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 variables, the covariate was categorized as shown in Table 11-1.

Table 11-1. Statistical Analysis for the Neurological Assessment

Dependent Variables

Variable	Data Source	Data Form	Cutpoints	Covariates[a]	Exclusions[b]	Statistical Analysis and Methods
Inflammatory Diseases	MR-V	D	Yes No	(1)	(a)	U:LR,CS A:LR
Hereditary and Degenerative Diseases	MR-V	D	Yes No	(1)	(a)	U:LR A:LR
Peripheral Disorders	MR-V	D	Yes No	(1)	(a)	U:LR A:LR
Other Neurological Disorders	MR-V	D	Yes No	(1)	(a)	U:LR A:LR
Smell	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
Visual Fields	PE	D	Abnormal Normal	(1)	(b)	U:LR,CS A:LR
Light Reaction	PE	D	Abnormal Normal	(1)	(b)	U:LR,CS A:LR
Ocular Movement	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
Facial Sensation	PE	D	Abnormal Normal	(1)	(b)	U:LR,CS A:LR
Corneal Reflex	PE	D	Abnormal Normal	--	--	Descriptive
Jaw Clench	PE	D	Deviated Symmetric	(1)	(b)	U:LR,CS A:LR
Smile	PE	D	Abnormal Normal	(1)	(b)	U:LR,CS A:LR
Palpebral Fissure	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
Balance	PE	D	Abnormal Normal	(1)	(b)	U:LR,CS A:LR
Gag Reflex	PE	D	Abnormal Normal	--	--	Descriptive
Speech	PE	D	Abnormal Normal	(1)	(b)	U:LR,CS A:LR
Tongue Position Relative to Midline	PE	D	Deviated Symmetric	(1)	(b)	U:LR,CS A:LR
Palate and Uvula Movement	PE	D	Deviated Symmetric	(1)	(b)	U:LR,CS A:LR

Table 11-1. Statistical Analysis for the Neurological Assessment (Continued)

Variable	Data Source	Data Form	Cutpoints	Covariates[a]	Exclusions[b]	Statistical Analysis and Methods
Cranial Nerve Index	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR L:LR
Neck Range of Motion	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
Pinprick	PE	D	Abnormal Normal	(1)	(c)	U:LR A:LR
Light Touch	PE	D	Abnormal Normal	(1)	(c)	U:LR A:LR
Muscle Status	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
Patellar Reflex	PE	D	Abnormal Normal	(1)	(d)	U:LR A:LR
Achilles Reflex	PE	D	Abnormal Normal	(1)	(e)	U:LR A:LR
Biceps Reflex	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
Babinski Reflex	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
Polyneuropathy Severity Index	PE	D	Severe Moderate None/Mild	(1)	(f)	U:PR A:PR
Polyneuropathy Prevalence Index	PE	D	Abnormal Normal	(1)	(f)	U:LR A:LR
Multiple Polyneuropathy Index	PE	D	Abnormal Normal	(1)	(f)	U:LR A:LR
Confirmed Polyneuropathy Indicator	PE	D	Abnormal Normal	(2)	(f)	U:LR,CS A:LR
Tremor	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
Coordination	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
Romberg Sign	PE	D	Abnormal Normal	(1)	(b)	U:LR,CS A:LR
Gait	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR
CNS Index	PE	D	Abnormal Normal	(1)	(b)	U:LR A:LR L:LR

[a]Covariates:

(1) Age, race, military occupation, lifetime alcohol history, insecticide exposure, industrial chemical exposure, degreasing chemical exposure, diabetic class.

(2) Age, race, military occupation, lifetime alcohol history, insecticide exposure, industrial chemical exposure, degreasing chemical exposure, diabetic class, composite exposure to heavy metals, worked with vibrating power equipment or tools.

Table 11-1. Statistical Analysis for the Neurological Assessment (Continued)

[b]Exclusions:

(a) Participants with positive serological tests for syphilis, participants who tested positive for HIV, participants with a verified pre-SEA history of the disorder.

(b) Participants with positive serological tests for syphilis, participants who tested positive for HIV.

(c) Participants with positive serological tests for syphilis, participants who tested positive for HIV, participants with peripheral edema of the lower extremities.

(d) Participants with positive serological tests for syphilis, participants who tested positive for HIV, participants with transient or sustained clonus of the patellar reflex.

(e) Participants with positive serological tests for syphilis, participants who tested positive for HIV, participants with transient or sustained clonus of the Achilles reflex.

(f) Participants with positive serological tests for syphilis, participants who tested positive for HIV, participants with peripheral edema of the lower extremities, participants with transient or sustained clonus of the Achilles reflex.

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
Lifetime Alcohol History (drink-years)	Q-SR	D/C	0 >0–40 >40
Insecticide Exposure	Q-SR	D	Yes No
Industrial Chemical Exposure	Q-SR	D	Yes No
Degreasing Chemical Exposure	Q-SR	D	Yes No
Diabetic Class	LAB/MR-V	D	• Diabetic: past history or ≥200 mg/dl 2-hr. postprandial glucose • Impaired: 140–<200 mg/dl 2-hr. postprandial glucose • Normal: <140 mg/dl 2-hr. postprandial glucose
Composite Exposure to Heavy Metals	Q-SR	D	Yes No
Worked With Vibrating Power Equipment or Tools	Q-SR	D	Yes No

Abbreviations

Data Source:
LAB: 1997 laboratory results
MIL: Air Force military records
MR-V: Medical records (verified)
PE: 1997 physical examination
Q-SR: Health questionnaire (self-reported)

Table 11-1. Statistical Analysis for the Neurological Assessment (Continued)

Data Form:
- D: Discrete analysis only
- D/C: Appropriate form for analysis (either discrete or continuous)

Statistical Analysis:
- U: Unadjusted analysis
- A: Adjusted analysis
- L: Longitudinal analysis

Statistical Methods:
- CS: Chi-square contingency table analysis (continuity-adjusted)
- LR: Logistic regression analysis
- PR: Polytomous logistic regression analysis

Table 11-2 provides a summary of the number of participants with missing dependent variable and covariate data. In addition, the number of participants excluded because of medical conditions is given.

Table 11-2. Number of Participants Excluded or with Missing Data for the Neurological Assessment

Variable	Variable Use	Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
		Ranch Hand	Comparison	Initial	1987	Ranch Hand	Comparison
Smell	DEP	4	2	2	4	4	2
Visual Fields	DEP	0	4	0	0	0	4
Light Reaction	DEP	5	2	1	5	5	2
Facial Sensation	DEP	1	1	0	1	1	1
Corneal Reflex	DEP	7	6	5	7	7	5
Balance	DEP	0	1	0	0	0	1
Gag Reflex	DEP	1	1	0	1	1	1
Cranial Nerve Index	DEP	16	4	7	16	16	4
Muscle Status	DEP	0	1	0	0	0	1
Patellar Reflex	DEP	1	2	1	1	1	1
Achilles Reflex	DEP	0	3	0	0	0	3
Biceps Reflex	DEP	0	1	0	0	0	1
Babinski Reflex	DEP	0	3	0	0	0	3
Polyneuropathy Severity Index	DEP	0	1	0	0	0	1
Multiple Polyneuropathy Index	DEP	1	0	1	1	1	0
Confirmed Polyneuropathy Index	DEP	14	10	7	13	13	9
Coordination	DEP	0	2	0	0	0	2
Romberg Sign	DEP	0	1	0	0	0	1
CNS Index	DEP	0	1	0	0	0	1
Lifetime Alcohol History	COV	6	2	3	6	6	1
Diabetic Class	COV	9	18	5	7	7	17
Worked with Vibrating Power Equipment or Tools	COV	1	2	1	1	1	2
Composite Exposure to Heavy Metals	COV	1	0	1	1	1	0
Pre-SEA Inflammatory Diseases	EXC	0	7	0	0	0	7

Table 11-2. Number of Participants Excluded or with Missing Data for the Neurological Assessment (Continued)

Variable	Variable Use	Group		Dioxin (Ranch Hands Only)		Categorized Dioxin	
		Ranch Hand	Comparison	Initial	1987	Ranch Hand	Comparison
Pre-SEA Peripheral Disorders	EXC	3	2	0	3	3	2
Pre-SEA Other Neurological Disorders	EXC	4	5	1	4	4	5
Positive Serological Test for Syphilis	EXC	1	0	0	1	1	0
HIV Positive	EXC	3	2	3	3	3	2
Peripheral Edema	EXC	45	64	26	45	45	62
Clonus – Patellar Reflex	EXC	0	1	0	0	0	1
Clonus – Achilles Reflex	EXC	1	2	0	1	1	2

Note: DEP = Dependent variable.
COV = Covariate.
EXC = Exclusion.
870 Ranch Hands and 1,251 Comparisons.
482 Ranch Hands for initial dioxin; 863 Ranch Hands for 1987 dioxin.
863 Ranch Hands and 1,213 Comparisons for categorized dioxin.

11.1.4.1 Longitudinal Analysis

The neurological longitudinal analyses were based on the cranial nerve index, excluding neck range of motion and the CNS index. Substantially fewer neurological abnormalities have been found in the 1985, 1987, 1992, and 1997 examinations than at the 1982 baseline examination, as noted in previous AFHS reports. This observation suggested that different techniques for the examination of the neurological system were used in 1982 than in the subsequent examinations. To enhance the comparability of measurements between examinations, the longitudinal assessment contrasted differences between the 1985 and 1997 neurological examinations.

11.2 RESULTS

11.2.1 Dependent Variable-Covariate Associations

The associations between the dependent variables examined in the neurological assessment and the covariates used in the adjusted analysis were investigated; the results are presented in Appendix F, Table F-3. These associations are pairwise between the dependent variable and the covariate and are not adjusted for any other covariates. Participants were excluded from each of the analyses as given in Table 11-1. Statistically significant associations are discussed below.

Age and industrial chemical exposure each exhibited significant associations with a history of hereditary and degenerative diseases (p=0.009 and p=0.022, respectively). Hereditary and degenerative diseases were greater for older participants than for younger participants (10.4% vs. 7.0%) and higher for participants reporting exposure to industrial chemicals than for those not reporting exposure (10.0% vs. 7.0%).

Tests of covariate associations with a history of peripheral disorders were significant for age ($p<0.001$), insecticide exposure ($p=0.014$), and diabetic class ($p<0.001$). Peripheral disorders were higher among older participants than younger participants (24.6% vs. 14.9%). Peripheral disorders were greater for participants exposed to insecticides (21.8%) than for participants not exposed to insecticides (16.9%), and greatest for diabetics (33.4%).

Several covariates were associated significantly with a history of other neurological disorders. Significant associations were found with age ($p<0.001$), race ($p<0.001$), occupation ($p<0.001$), industrial chemical exposure ($p<0.001$), degreasing chemical exposure ($p<0.001$), and diabetic class ($p<0.001$). Older participants had a greater history of other neurological disorders (22.0%) than did younger participants (13.4%). Blacks exhibited a greater history of other neurological disorders (33.1%) than did non-Blacks (17.3%). Other neurological disorders were highest for enlisted flyers (27.0%), followed by enlisted groundcrew (24.1%), and then by officers (8.1%). Participants reporting exposure to industrial chemicals and degreasing chemicals had more neurological disorders than participants who did not report exposure. Diabetics had the greatest history of other neurological disorders (23.9%).

Covariate association tests for the light reaction variable were significant for race ($p=0.046$). Blacks exhibited more light reaction abnormalities (2.3%) than did non-Blacks (0.5%).

Covariate association tests for smile, palpebral fissure, and balance were each significant for diabetic class ($p=0.030$, $p=0.007$, and $p=0.036$, respectively). For each variable, the most abnormalities were among diabetics, followed by those classified as normal, and then by those in the impaired diabetic category.

The neck range of motion variable was associated significantly with age ($p<0.001$), occupation ($p=0.006$), and diabetic class ($p=0.022$). A restricted range of motion was greater for older participants (22.0%) than for younger participants (9.9%). Enlisted flyers had the greatest prevalence of an abnormal neck range of motion (20.7%), followed by officers (18.1%), then enlisted groundcrew (14.0%). Diabetics displayed the highest prevalence of neck range of motion abnormalities (21.6%), followed by nondiabetics (15.6%), then by participants in the impaired diabetic category (15.4%).

Tests of covariate association for the cranial nerve index variable were significant for age ($p=0.004$) and diabetic class ($p=0.014$). An abnormal index was found in 7.5 percent of older participants and 4.4 percent of younger participants. More abnormalities were found as the level of diabetic impairment increased.

Covariate association tests were similar for the pinprick and light touch dependent variables. Each were associated significantly with age ($p=0.006$ and $p=0.022$, respectively), occupation ($p=0.006$ and $p=0.036$, respectively), and diabetic class ($p<0.001$ for both). Both variables displayed higher abnormalities among older participants, enlisted flyers, and diabetics.

The patellar reflex variable was associated significantly with age ($p<0.001$), race ($p=0.030$), and diabetic class ($p<0.001$). The higher abnormality prevalences were among older participants (4.0%, compared to 1.3% for younger participants), Blacks (6.3%, compared to 2.6% for non-Blacks), and diabetics (7.3%, compared to 2.6% for participants in the impaired category and 1.8% for nondiabetics).

Tests of covariate association for the Achilles reflex variable showed significant results for age ($p<0.001$), lifetime alcohol history ($p=0.027$), and diabetic class ($p<0.001$). Older participants had a higher prevalence of Achilles reflex abnormalities than did younger participants (22.8% vs. 9.3%). The

heaviest drinkers (in terms of drink-years) had an abnormal Achilles reflex most often (20.2%), followed by nondrinkers (18.6%), and moderate drinkers (15.4%). Achilles reflex abnormalities increased as the level of diabetic impairment increased (nondiabetic: 13.4%; impaired: 16.2%; diabetic: 31.9%).

An abnormal biceps reflex was associated significantly with diabetic class (p=0.007), where the prevalence of biceps reflex abnormalities increased as the level of diabetic impairment increased.

Tests of covariate association for the polyneuropathy severity index were significant for age (p=0.002), race (p=0.005), and diabetic class (p<0.001). Older participants displayed a greater percentage of moderate and severe index scores (2.6% and 0.4%, respectively) than younger participants (0.7% and 0.1%, respectively). Non-Blacks displayed the higher moderate index score (1.8%), while Blacks displayed the higher severe index score (1.6%). Diabetics exhibited the highest percentage of both the moderate and severe index scores (5.9% and 0.9%, respectively), followed by nondiabetics (0.9% and 0.1%, respectively). Participants in the impaired diabetic category displayed the smallest percentage of moderate and severe index scores (0.4% and 0.0%, respectively).

Covariate tests of association for the polyneuropathy prevalence index revealed significant associations with age, occupation, lifetime alcohol history, and diabetic class (p<0.001 for each). The percentage of abnormal polyneuropathy prevalence index results increased with age, lifetime alcohol history, and level of diabetic impairment. Enlisted flyers had the highest percentage of abnormal polyneuropathy prevalence index results (20.8%), followed by officers (16.5%), then enlisted groundcrew (12.5%).

The multiple polyneuropathy index variable was significantly associated with age (p<0.001), occupation (p=0.006), and diabetic class (p<0.001). The percentage of abnormal multiple polyneuropathy index findings increased with age. Enlisted flyers had the highest percentage of abnormalities (6.7%), followed by officers (4.2%), and enlisted groundcrew (2.7%). Diabetic participants had the highest prevalence of abnormal results (12.7%), followed by nondiabetics (2.4%), and participants in the impaired diabetic class (1.2%).

Age and diabetic classes were associated significantly with the confirmed polyneuropathy indicator variable (p=0.007 and p<0.001, respectively). Older participants had a higher percentage of abnormal findings than did younger participants (1.5% vs. 0.2%). Diabetic participants had the highest prevalence of confirmed polyneuropathy results (2.9%), followed by nondiabetics (0.6%), then participants in the impaired diabetic class (0.0%).

Insecticide exposure and industrial chemical exposure both were significantly associated with tremor (p=0.003 and p=0.004, respectively). Participants reporting exposure to insecticides had a higher percentage of tremors than participants who did not report exposure (8.2% vs. 4.5%). Similarly, participants reporting exposure to industrial chemicals had a higher prevalence of tremors than those who did not report exposure (8.4% vs. 5.0%).

Tests of covariate association for coordination revealed diabetic class to be significant (p=0.013). Abnormality rates increased as the level of diabetic impairment increased.

Diabetic class was significantly associated with Romberg sign (p=0.036). Diabetic participants had the highest percentage of abnormal Romberg sign results (1.7%), followed by nondiabetics (0.5%), and participants in the impaired diabetic class (0.4%).

Age and diabetic classes were associated significantly with gait ($p<0.001$ for each). Older participants had a higher percentage of an abnormal gait than did younger participants (6.8% vs. 2.8%). The prevalence of a gait abnormality increased with diabetic impairment.

Tests of covariate association for the CNS index revealed significant associations with age ($p<0.001$), insecticide exposure ($p<0.001$), and industrial chemical exposure ($p=0.021$). The percentage of participants with an abnormal index increased with age. Participants reporting exposure to insecticides had a higher percentage of abnormal CNS index results than did participants who did not report exposure (13.7% vs. 8.2%). Similarly, participants reporting exposure to industrial chemicals had a higher prevalence of abnormal results than those who did not report exposure (13.4% vs. 9.9%).

11.2.2 Exposure Analysis

The following section presents results of the statistical analysis of the dependent variables shown in Table 11-1. Dependent variables were derived from a medical records review and verification and a neurological examination to assess the cranial nerve function, peripheral nerve status, and CNS coordination processes.

Four models were examined for each dependent variable given in Table 11-1. The analyses of these models are presented below. Further details on dioxin and the modeling strategy are found in Chapters 2 and 7, respectively. These analyses were performed both unadjusted and adjusted for relevant covariates. Model 1 examined the relation between the dependent variable and group (i.e., Ranch Hand or Comparison). In this model, exposure was defined as "yes" for Ranch Hands and "no" for Comparisons without regard to the magnitude of the exposure. As an attempt to quantify exposure, three contrasts of Ranch Hands and Comparisons were performed along with the overall Ranch Hand versus Comparison contrast. These three contrasts compared Ranch Hands and Comparisons within each occupational category (i.e., officers, enlisted flyers, and enlisted groundcrew). As described in previous reports, the average levels of exposure to dioxin were highest for enlisted groundcrew, followed by enlisted flyers, and 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 (43).

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.

11.2.2.1 Medical Records Variables

11.2.2.1.1 Inflammatory Diseases

A significant difference in the history of inflammatory diseases between Ranch Hands and Comparisons was revealed in both the unadjusted and adjusted analyses (Table 11-3(a,b): Est. RR=10.11, p=0.006; and Adj. RR=13.50, p=0.002, respectively). Seven Ranch Hands (0.8%) and one Comparison (0.1%) have had an inflammatory disease. Of the seven Ranch Hands with inflammatory diseases, three had meningitis caused by bacterial infections, three had meningitis of unknown cause, and one had encephalitis of unknown cause. The single Comparison with an inflammatory disease had encephalitis of unknown cause. All other Model 1 contrasts, as well as the Model 2 results, were nonsignificant (Table 11-3(a–d): p>0.11 for each Model 1 and Model 2 analysis).

Table 11-3. Analysis of Inflammatory Diseases

(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***	***866***	***7 (0.8)***	***10.11 (1.24,82.35)***	***0.006***
	Comparison	***1,242***	***1 (0.1)***		
Officer	Ranch Hand	340	2 (0.6)	--	0.327[a]
	Comparison	490	0 (0.0)		
Enlisted Flyer	Ranch Hand	151	2 (1.3)	--	0.391[a]
	Comparison	185	0 (0.0)		
Enlisted Groundcrew	Ranch Hand	375	3 (0.8)	4.56 (0.47,44.05)	0.189
	Comparison	567	1 (0.2)		

[a] P-value determined using a chi-square test with continuity correction because of the sparse number of participants with a history of an inflammatory disease.
--: Results not presented because of the sparse number of participants with an inflammatory disease.

Table 11-3. Analysis of Inflammatory Diseases (Continued)

(b) MODEL 1: RANCH HANDS VS. COMPARISONS – ADJUSTED		
Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	***13.50 (1.61,113.13)***	***0.002***
Officer	--	--
Enlisted Flyer	--	--
Enlisted Groundcrew	6.38 (0.64,63.30)	0.114

--: Results not presented because of the sparse number of participants with an inflammatory disease.

Note: Results are not adjusted for race and diabetic class because of the sparse number of participants with an inflammatory disease.

(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	160	2 (1.3)	1.03 (0.48,2.18)	0.943
Medium	162	1 (0.6)		
High	157	1 (0.6)		

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

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

(d) MODEL 2: RANCH HANDS – INITIAL DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (Initial Dioxin)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
476	0.98 (0.45,2.17)	0.964

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

Note: Results are not adjusted for race, occupation, industrial chemicals exposure, degreasing chemicals exposure, and diabetic class because of the sparse number of participants with an inflammatory disease.

Table 11-3. Analysis of Inflammatory Diseases (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	1,204	1 (0.1)		
Background RH	380	3 (0.8)	8.82 (0.91,85.93)	0.061
Low RH	239	2 (0.8)	10.31 (0.93,114.27)	0.057
High RH	240	2 (0.8)	10.86 (0.97,121.25)	0.053
Low plus High RH	479	4 (0.8)	10.58 (1.18,95.25)	0.035

[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	1,203		
Background RH	377	13.28 (1.31,135.01)	0.029
Low RH	238	13.85 (1.20,160.07)	0.035
High RH	238	12.43 (1.03,149.42)	0.047
Low plus High RH	476	13.12 (1.39,123.67)	0.024

[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.

Results are not adjusted for race and diabetic class because of the sparse number of participants with an inflammatory disease.

(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	287	2 (0.7)	0.97 (0.58,1.63)	0.920
Medium	287	3 (1.1)		
High	285	2 (0.7)		

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

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

Table 11-3. Analysis of Inflammatory Diseases (Continued)

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (1987 Dioxin + 1)	
	Adjusted Relative Risk	
n	(95% C.I.)[a]	p-Value
853	0.90 (0.52,1.57)	0.716

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

Note: Results are not adjusted for race and diabetic class because of the sparse number of participants with an inflammatory disease.

The Model 3 unadjusted analysis of history of inflammatory diseases revealed marginally significant differences for each contrast involving Ranch Hands in the background, low, and high dioxin categories (Table 11-3(e): Est. RR=8.82, p=0.061; Est. RR=10.31, p=0.057; and Est. RR=10.86, p=0.053, respectively). The remaining unadjusted contrast combining Ranch Hands in the low plus high dioxin category revealed significant differences between Ranch Hands and Comparisons (Table 11-3(e): Est. RR=10.58, p=0.035). Each Model 3 contrast was significant in the adjusted analysis, and each also displayed more Ranch Hands than Comparisons with inflammatory diseases (Table 10-3(f): Adj. RR=13.28, p=0.029; Adj. RR=13.85, p=0.035; Adj. RR=12.43, p=0.047; and Adj. RR=13.12, p=0.024).

Both the unadjusted and adjusted Model 4 analyses of inflammatory diseases were nonsignificant (Table 11-3(g,h): p>0.71 for each Model 4 analysis).

11.2.2.1.2 Hereditary and Degenerative Diseases

All results from Models 1 through 4 for hereditary and degenerative diseases were nonsignificant (Table 11-4(a–h): p≥0.38 for each analysis).

Table 11-4. Analysis of Hereditary and Degenerative Diseases

(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***	***866***	***80 (9.2)***	***1.08 (0.79,1.46)***	***0.639***
	Comparison	***1,249***	***108 (8.7)***		
Officer	Ranch Hand	340	30 (8.8)	1.19 (0.72,1.97)	0.492
	Comparison	493	37 (7.5)		
Enlisted Flyer	Ranch Hand	151	19 (12.6)	1.27 (0.65,2.50)	0.484
	Comparison	187	19 (10.2)		
Enlisted Groundcrew	Ranch Hand	375	31 (8.3)	0.90 (0.56,1.43)	0.643
	Comparison	569	52 (9.1)		

Table 11-4. Analysis of Hereditary and Degenerative Diseases (Continued)

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	***1.07 (0.78,1.46)***	***0.688***
Officer	1.13 (0.68,1.89)	0.635
Enlisted Flyer	1.31 (0.66,2.62)	0.444
Enlisted Groundcrew	0.92 (0.57,1.48)	0.737

(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	160	17 (10.6)	1.01 (0.79,1.28)	0.952
Medium	162	12 (7.4)		
High	157	14 (8.9)		

[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

Analysis Results for Log_2 (Initial Dioxin)		
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
471	1.02 (0.76,1.36)	0.909

[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	1,211	107 (8.8)		
Background RH	380	37 (9.7)	1.08 (0.73,1.61)	0.697
Low RH	239	21 (8.8)	1.00 (0.61,1.63)	0.999
High RH	240	22 (9.2)	1.07 (0.66,1.73)	0.792
Low plus High RH	479	43 (9.0)	1.03 (0.71,1.50)	0.864

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

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

Table 11-4. Analysis of Hereditary and Degenerative Diseases (Continued)

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

Dioxin Category	n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
Comparison	1,193		
Background RH	375	1.16 (0.77,1.76)	0.474
Low RH	235	0.92 (0.56,1.52)	0.736
High RH	236	1.01 (0.61,1.67)	0.979
Low plus High RH	471	0.96 (0.65,1.41)	0.841

[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	287	27 (9.4)	0.96 (0.82,1.12)	0.590
Medium	287	30 (10.5)		
High	285	23 (8.1)		

[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
846	0.92 (0.77,1.11)	0.380

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

11.2.2.1.3 Peripheral Disorders

Results from the Model 1 analysis of history of peripheral disorders displayed no significant differences between Ranch Hands and Comparisons (Table 11-5(a,b): $p>0.11$ for each unadjusted and adjusted contrast). The unadjusted and adjusted results from the Model 2 analysis also did not display a significant relation between peripheral disorders and initial dioxin (Table 11-5(c,d): $p\geq0.40$ for the unadjusted and adjusted Model 2 analysis).

Table 11-5. Analysis of Peripheral Disorders

(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***	***863***	***188 (21.8)***	***1.16 (0.94,1.44)***	***0.169***
	Comparison	***1,247***	***241 (19.3)***		
Officer	Ranch Hand	339	78 (23.0)	1.32 (0.94,1.85)	0.113
	Comparison	492	91 (18.5)		
Enlisted Flyer	Ranch Hand	150	36 (24.0)	1.02 (0.62,1.69)	0.941
	Comparison	186	44 (23.7)		
Enlisted Groundcrew	Ranch Hand	374	74 (19.8)	1.08 (0.77,1.50)	0.658
	Comparison	569	106 (18.6)		

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	***1.12 (0.89,1.40)***	***0.341***
Officer	1.25 (0.88,1.78)	0.215
Enlisted Flyer	0.91 (0.54,1.54)	0.733
Enlisted Groundcrew	1.09 (0.77,1.54)	0.622

(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	160	40 (25.0)	1.01 (0.86,1.18)	0.915
Medium	162	42 (25.9)		
High	157	38 (24.2)		

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

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

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

Analysis Results for Log_2 (Initial Dioxin)		
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
471	1.09 (0.90,1.32)	0.400

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

Table 11-5. Analysis of Peripheral Disorders (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	1,209	233 (19.3)		
Background RH	377	65 (17.2)	0.91 (0.67,1.23)	0.531
Low RH	239	61 (25.5)	1.42 (1.03,1.97)	0.033
High RH	240	59 (24.6)	1.32 (0.95,1.83)	0.097
Low plus High RH	479	120 (25.1)	1.37 (1.07,1.76)	0.014

[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	1,191		
Background RH	372	0.88 (0.64,1.21)	0.437
Low RH	235	1.25 (0.89,1.76)	0.190
High RH	236	1.33 (0.94,1.90)	0.111
Low plus High RH	471	1.29 (0.99,1.69)	0.059

[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	285	44 (15.4)	1.15 (1.04,1.29)	0.010
Medium	286	71 (24.8)		
High	285	70 (24.6)		

[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.

Table 11-5. Analysis of Peripheral Disorders (Continued)

(h) MODEL 4: RANCH HANDS – 1987 DIOXIN – ADJUSTED		
	Analysis Results for Log_2 (1987 Dioxin + 1)	
	Adjusted Relative Risk	
n	(95% C.I.)[a]	p-Value
843	1.20 (1.04,1.38)	0.011

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

The Model 3 unadjusted analysis indicated a significantly greater percentage of Ranch Hands in the low dioxin category than Comparisons with a peripheral disorder (Table 11-5(e): Est. RR=1.42, p=0.033). The result was nonsignificant after adjustment for covariates (Table 11-5(f): p=0.190). The unadjusted analysis also revealed a marginally significant increase for the Ranch Hands in the high dioxin category (Table 11-5(e): Est. RR=1.32, p=0.097). This result was nonsignificant in the adjusted analysis (Table 11-5(f): p=0.111). The contrast of Ranch Hands in the low plus high dioxin category with Comparisons displayed a significant difference in the percentage of participants with a peripheral disorder (Table 11-5(e): Est. RR=1.37, p=0.014), indicating a greater occurrence of peripheral disorders among Ranch Hands than Comparisons. The result was marginally significant after adjustment for covariates (Table 11-5(f): Adj. RR=1.29, p=0.059).

The Model 4 unadjusted and adjusted analyses each displayed a significant association between peripheral disorders and 1987 dioxin levels (Table 11-5(g): Est. RR=1.15, p=0.010; and Adj. RR=1.20, p=0.011, respectively). The occurrence of peripheral disorders increased as 1987 dioxin increased.

11.2.2.1.4 Other Neurological Disorders

A marginally significant increase in a history of other neurological disorders was found in Ranch Hands relative to Comparisons in the Model 1 analyses, both unadjusted and adjusted (Table 11-6(a,b): Est. RR=1.23, p=0.070; and Adj. RR=1.25, p=0.078). When differences were examined within each occupation, the results were nonsignificant in both the unadjusted and adjusted analyses (Table 11-6(a,b): p>0.13 for each contrast). Each Model 2 analysis also was nonsignificant (Table 11-6(c,d): p>0.48 for both analyses).

Table 11-6. Analysis of Other Neurological Disorders

(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***	***862***	***173 (20.1)***	***1.23 (0.98,1.54)***	***0.070***
	Comparison	***1,244***	***211 (17.0)***		
Officer	Ranch Hand	338	29 (8.6)	1.12 (0.68,1.86)	0.656
	Comparison	492	38 (7.7)		
Enlisted Flyer	Ranch Hand	151	46 (30.5)	1.37 (0.85,2.22)	0.198
	Comparison	186	45 (24.2)		
Enlisted Groundcrew	Ranch Hand	373	98 (26.3)	1.22 (0.90,1.65)	0.200
	Comparison	566	128 (22.6)		

Table 11-6. Analysis of Other Neurological Disorders (Continued)

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	***1.25 (0.98,1.59)***	***0.078***
Officer	1.09 (0.65,1.84)	0.734
Enlisted Flyer	1.33 (0.79,2.21)	0.283
Enlisted Groundcrew	1.28 (0.92,1.78)	0.136

(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	160	34 (21.3)	1.06 (0.90,1.24)	0.483
Medium	161	41 (25.5)		
High	157	38 (24.2)		

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

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

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

	Analysis Results for Log_2 (Initial Dioxin)	
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
470	0.99 (0.81,1.20)	0.922

[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.)[a,b]	p-Value
Comparison	1,206	204 (16.9)		
Background RH	377	59 (15.7)	0.88 (0.64,1.21)	0.442
Low RH	239	55 (23.0)	1.48 (1.06,2.07)	0.023
High RH	239	58 (24.3)	1.62 (1.16,2.26)	0.005
Low plus High RH	478	113 (23.6)	1.55 (1.19,2.01)	0.001

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

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

Table 11-6. Analysis of Other Neurological Disorders (Continued)

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

Dioxin Category	n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
Comparison	1,188		
Background RH	372	1.21 (0.85,1.73)	0.281
Low RH	235	1.31 (0.90,1.89)	0.161
High RH	235	1.23 (0.85,1.77)	0.271
Low plus High RH	470	1.27 (0.95,1.69)	0.106

[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	285	45 (15.8)	1.13 (1.01,1.26)	0.038
Medium	286	54 (18.9)		
High	284	73 (25.7)		

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

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

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

Analysis Results for Log_2 (1987 Dioxin + 1)		
n	Adjusted Relative Risk (95% C.I.)[a]	p-Value
443	0.97 (0.84,1.11)	0.625

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

The Model 3 unadjusted analysis displayed significant differences between Ranch Hands in each of the low, high, and low plus high dioxin categories and Comparisons (Table 11-6(e): Est. RR=1.48, p=0.023; Est. RR=1.62, p=0.005; and Est. RR=1.55, p=0.001, respectively). Each result became nonsignificant after adjustment for covariates (Table 11-6(f): p>0.10 for each adjusted result). The Model 3 contrast of Ranch Hands in the background dioxin category with Comparisons was nonsignificant in both the unadjusted and adjusted analysis (Table 11-6(g,h): p>0.28 for the unadjusted and adjusted analyses).

A significant positive association between other neurological disorders and the 1987 dioxin levels was found in the Model 4 unadjusted analysis (Table 11-6(g): Est. RR=1.13, p=0.038). After adjustment for covariates, the association became nonsignificant (Table 11-6(h): p=0.625).

11.2.2.2 Physical Examination Variables – Cranial Nerve Function

11.2.2.2.1 Smell

A marginally significant difference was found between Ranch Hand and Comparison enlisted flyers from the Model 1 unadjusted analysis of an abnormal sense of smell (Table 11-7(a): Est. RR=7.70, p=0.060). After adjustment for covariates, the result was nonsignificant (Table 11-7(b): p=0.148). All other Model 1 contrasts, as well as all other results from Models 2 through 4, were nonsignificant (Table 11-7(a–h): p>0.12 for each remaining analysis).

Table 11-7. Analysis of Smell

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

Occupational Category	Group	n	Number (%) Abnormal	Est. Relative Risk (95% C.I.)	p-Value
All	***Ranch Hand***	***862***	***20 (2.3)***	***1.54 (0.81,2.89)***	***0.186***
	Comparison	***1,247***	***19 (1.5)***		
Officer	Ranch Hand	337	5 (1.5)	0.73 (0.25,2.14)	0.562
	Comparison	492	10 (2.0)		
Enlisted Flyer	Ranch Hand	151	6 (4.0)	7.70 (0.92,64.65)	0.060
	Comparison	187	1 (0.5)		
Enlisted Groundcrew	Ranch Hand	374	9 (2.4)	1.73 (0.66,4.51)	0.266
	Comparison	568	8 (1.4)		

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

Occupational Category	Adjusted Relative Risk (95% C.I.)	p-Value
All	***1.20 (0.60,2.36)***	***0.609***
Officer	0.53 (0.16,1.71)	0.286
Enlisted Flyer	5.12 (0.56,46.70)	0.148
Enlisted Groundcrew	1.57 (0.58,4.27)	0.376

(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 (%) Abnormal	Estimated Relative Risk (95% C.I.)[b]	p-Value
Low	159	5 (3.1)	0.94 (0.58,1.51)	0.782
Medium	162	2 (1.2)		
High	156	4 (2.6)		

[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.