TABLE 10-17.

Summary of Followup Participants With Lifetime Incidence of Verified Malignant Systemic Neoplasms by Group

Site	Group		Total
	Ranch Hand	Comparison	
Eye	1	0	1
Oral Cavity and Pharynx	3[a,b]	0	3
Larynx	0	1	1
Thyroid Gland	0	2	2
Esophagus	0	1[c]	1
Bronchus and Lung	2	0	1
Colon	0	5[d,•]	5
Kidney and Bladder	4	3	7
Prostate	2	2	4
Testicles	3	0	3
Connective and Other Soft Tissue	1	1	2
Hodgkin's Disease	0	1	1
Ill-Defined Sites	1[f]	1[g]	2
Total	17	17	34

[a]Includes one Ranch Hand with separate malignancies of tongue and epiglottis and also malignant neoplasm of bone.

[b]Includes one Ranch Hand with separate malignant neoplasms of tongue and oropharynx and secondary malignant neoplasm of other site.

[c]Also has malignant neoplasm of bone.

[d]Incudes one Comparison with secondary malignant neoplasms of liver and bone and bone marrow.

[•]Includes one Comparison with secondary malignant neoplasm of liver.

[f]Malignant neoplasm of thorax.

[g]Malignant neoplasm of face, head, or neck.

One Ranch Hand and one Comparison had neoplasms of connective and other soft tissue. The Comparison had a fibrosarcoma at age 28 (reported at Baseline) and the Ranch Hand participant had malignant fibrous histiocytoma at age 63 (reported at followup). Both of these conditions are classified as soft tissue sarcoma.

Since soft tissue sarcoma and malignant neoplasms of the lymphatic system are of concern in this study, the occurrences of these malignancies are shown by group in Table 10-18. The occurrences of these four malignancies are too small to support further statistical analysis.

TABLE 10-18.

Summary of Followup Participants with Lifetime Soft Tissue Sarcoma, Leukemia or Lymphoma by Group

Site	Group	
	Ranch Hand	Comparison
Verified Soft Tissue Sarcoma	1	1
Verified Hodgkin's Disease	0	1
Suspected Leukemia, Hodgkin's Disease, or non-Hodgkin's Lymphoma	1	0

Unadjusted Analysis

Table 10-19 shows the results of unadjusted analyses of the frequencies of participants in each group with verified or verified plus suspected malignant systemic neoplasms combined. The estimated relative risk for all malignant systemic neoplasms was 1.28 (95% C.I.: 0.65,2.51) and was not significant (p=0.491). With the inclusion of suspected malignant neoplasms, the estimated relative risk was 1.22 (95% C.I.: 0.67,2.23) and was also not significant (p=0.538). Similar nonsignificant results were found for Ranch Hands contrasted with Original Comparisons (see Table H-22 of Appendix H).

Covariates

The same covariates used for the interval history of malignant systemic neoplasms were used for the adjusted analysis of lifetime malignant systemic neoplasms, namely, age, race, occupation, history of cigarette smoking and alcohol consumption, and exposure to carcinogens. Total smoking and alcohol consumption were estimated up to the followup examination, and may be different if estimated only up to the year of diagnosis of a neoplasm (if any). Further, age at followup rather than age at diagnosis was used in the analysis.

TABLE 10-19.

Unadjusted Analyses of Lifetime Incidence Rates
of All Malignant Systemic Neoplasms Combined, by Group

Status	Statistic	Group: Ranch Hand		Group: Comparison		Est. Relative Risk (95% C.I.)	p-Value
Verified	Number of Participants/%	17	1.7%	17	1.3%	1.28 (0.65, 2.51)	0.491
	Total Neoplasms	25		22			
Verified & Suspected	Number of Participants/%	21	2.1%	22	1.7%	1.22 (0.67,2.23)	0.538
	Total Neoplasms	36		27			

Covariate Associations

Associations between the incidence rate of all malignant systemic neoplasms combined and the covariates are presented in Table 10-20. For verified malignant systemic neoplasms, strong associations were found with increasing age ($p<0.001$) and occupation (officers 2.3%, enlisted flyers 1.3%, and enlisted groundcrew 0.9%, $p=0.028$). These same associations were also found for verified plus suspected systemic malignancies. The association with smoking history was not significant, either for verified or for verified plus suspected malignancies. The incidence rate of all malignant systemic neoplasms increased marginally significantly ($p=0.073$) with increasing levels of total lifetime alcohol consumption. For verified plus suspected malignancies, the difference among drink-year categories was also marginally significant ($p=0.080$). No significant association was found with the composite carcinogen exposure variable. A significant association was found between the incidence of verified malignant systemic neoplasms and naphthylamine ($p=0.048$). There was a significant positive association between the verified plus suspected conditions and naphthylamine ($p=0.019$), and a marginally significant association with chloromethyl ether ($p=0.067$).

The covariates used for the adjusted analysis of the incidence of malignant systemic neoplasms were race, age (continuous), occupation, pack-years, drink-years, and the composite carcinogen-exposure variable.

Adjusted Analysis

Table 10-21 shows that, in the adjusted analysis of the group contrast in incidence of all systemic malignancies combined, there was a significant group-by-occupation interaction ($p=0.023$). This was due to a difference in rates for the enlisted flyers, 5 Ranch Hands versus 0 Comparisons (unadjusted p-value=0.019), whereas the incidence rates for officers and enlisted groundcrew did not differ significantly between groups ($p=0.698$ and 0.922, respectively) (Table H-23). Age made a significant contribution to the adjustment. When suspected systemic malignancies were combined with the verified systemic malignancies, a group-by-occupation interaction ($p=0.002$)

TABLE 10-20.

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified			Verified and Suspected		
			Number*	Percent	p-Value	Number*	Percent	p-Value
Age	Born ≥1942	961	4	0.4	<0.001	7	0.7	<0.001
	Born 1923-41	1,261	24	1.9		30	2.4	
	Born ≤1922	87	6	6.9		6	6.9	
Race	Nonblack	2,166	34	1.6	0.267	42	1.9	0.517
	Black	143	0	0.0		1	0.7	
Occupation	Officer	864	20	2.3	0.028	23	2.7	0.069
	Enlisted Flyer	387	5	1.3		7	1.8	
	Enlisted Groundcrew	1,058	9	0.9		13	1.2	
Total Lifetime Smoking (Pack-Years)	0	658	6	0.9	0.237	8	1.2	0.324
	>0-20	1,081	15	1.4		20	1.9	
	>20-40	406	9	2.2		11	2.7	
	>40	158	4	2.5		4	2.5	
Total Lifetime Alcohol Consumption (Drink-Years)	0	151	1	0.7	0.073	2	1.3	0.080
	>0-5	760	7	0.9		10	1.3	
	>5-30	703	8	1.1		10	1.4	
	>30-100	508	11	2.2		13	2.6	
	>100	108	4	3.7		5	4.6	

TABLE 10-20. (continued)

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants		Verified Number*	Verified Percent	Verified p-Value	Verified and Suspected Number*	Verified and Suspected Percent	Verified and Suspected p-Value
Exposures to Carcinogens	Asbestos	499	Yes	5	1.0	0.405	7	1.4	0.459
		1,810	No	29	1.6		36	2.0	
	Nonmedical X Rays	541	Yes	9	1.7	0.684	14	2.6	0.150
		1,768	No	25	1.4		29	1.6	
	Industrial Chemicals	1,199	Yes	14	1.2	0.229	20	1.7	0.539
		1,110	No	20	1.8		23	2.1	
	Herbicides	1,339	Yes	18	1.3	0.601	23	1.7	0.538
		970	No	16	1.7		20	2.1	
	Insecticides	1,389	Yes	17	1.2	0.223	23	1.7	0.432
		920	No	17	1.9		20	2.2	
	Degreasing Chemicals	1,343	Yes	18	1.3	0.600	26	1.9	0.876
		966	No	16	1.7		17	1.8	
Composite Carcinogen Exposure		519	Yes	7	1.4	0.999	8	1.5	0.711
		1,762	No	27	1.5		34	1.9	

TABLE 10-20. (continued)

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified				Verified and Suspected		
				Number*	Percent	p-Value	Number*	Percent	p-Value
Exposure to Individual Carcinogens	Anthracene	2	Yes	0	0.0	0.999	0	0.0	0.999
		2,303	No	34	1.5		43	1.9	
	Arsenic	42	Yes	0	0.0	0.999	2	4.8	0.183
		2,266	No	34	1.5		41	1.8	
	Benzene	83	Yes	2	2.4	0.348	2	2.4	0.666
		2,225	No	32	1.4		41	1.8	
	Benzidine	14	Yes	1	7.1	0.188	1	7.1	0.227
		2,293	No	33	1.4		41	1.8	
	Chromates	88	Yes	2	2.3	0.375	2	2.3	0.679
		2,218	No	32	1.4		41	1.9	
	Coal Tar	73	Yes	2	2.7	0.292	2	2.7	0.397
		2,235	No	32	1.4		41	1.8	
	Creosote	164	Yes	2	1.2	0.999	4	2.4	0.543
		2,145	No	32	1.5		39	1.8	
	Aminodiphenyl	6	Yes	0	0.0	0.999	1	16.7	0.107
		2,300	No	34	1.5		42	1.8	
	Chloromethyl Ether	23	Yes	1	4.4	0.291	2	8.7	0.067
		2,282	No	33	1.5		41	1.8	
	Mustard Gas	9	Yes	0	0.0	0.999	1	11.1	0.156
		2,299	No	34	1.5		42	1.8	

TABLE 10-20. (continued)

Association Between Lifetime Incidence of All Malignant Systemic Neoplasms Combined and the Covariates for Combined Followup Ranch Hand and Comparison Participants

Covariate	Category	Total Participants	Verified				Verified and Suspected		
				Number*	Percent	p-Value	Number*	Percent	p-Value
Exposure to Individual Carcinogens (continued)	Naphthylamine	56	Yes	3	5.4	0.048	4	7.1	0.019
		2,251	No	31	1.4		39	1.7	
	Cutting Oils	243	Yes	5	2.1	0.396	7	2.9	0.209
		2,065	No	29	1.4		36	1.7	
	Trichloroethylene	200	Yes	5	2.5	0.211	6	3.0	0.264
		2,106	No	29	1.4		37	1.8	
	Ultraviolet Light	51	Yes	1	2.0	0.535	1	2.0	0.621
		2,256	No	33	1.5		42	1.9	
	Vinyl Chloride	33	Yes	0	0.0	0.999	1	3.0	0.465
		2,273	No	34	1.5		42	1.9	

*Number of participants with malignant systemic neoplasms.

TABLE 10-21.

Adjusted Analyses for Lifetime Incidence of All Malignant Systemic Neoplasms Combined

Variable	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Systemic Malignancies (Verified)	****	****	GRP*OCC (p=0.023) AGE (p<0.001)
Systemic Malignancies (Verified & Suspected)	****	****	GRP*OCC (p=0.002) AGE (p<0.001) RACE*PACKYR (p=0.032)

****Group-by-covariate interaction--adjusted relative risk, confidence interval, and p-value not presented.

was also found; this was also due to the high rates for the Ranch Hand enlisted flyers.

Comparison of Baseline, Interval, and Lifetime Results

Table 10-22 compares the unadjusted and adjusted contrasts from the Baseline report with those from the Baseline-followup interval and the whole post-SEA period, for the incidence of all verified malignant skin neoplasms combined, verified basal cell carcinomas, and all verified malignant systemic neoplasms combined. There were, of course, differences in the Baseline and followup cohorts, but there was a sufficiently large overlap to make such a comparative tabulation useful.

Malignant Skin Neoplasms

The significant relative risks for all malignant skin neoplasms seen at Baseline were not evident for the Baseline-followup interval. However, for lifetime basal cell carcinoma, a significant adjusted group contrast was found (p=0.035). The difference in the incidence rates of all skin neoplasms and in basal cell carcinomas only between the Ranch Hands and the Comparisons appears to have decreased over time, as evidenced by the fact that the interval estimated and adjusted relative risks were closer to 1 than those for the lifetime, i.e., interval plus Baseline period.

Malignant Systemic Neoplasms

The unadjusted group contrasts in incidence rates of all malignant systemic neoplasms combined were not significant for Baseline, for the Baseline-followup interval, or for lifetime (Baseline plus interval), nor was the adjusted group contrast for the Baseline-followup interval. The

TABLE 10-22.

Unadjusted and Adjusted Analyses of the Incidence of All Verified Malignant Skin and Systemic Neoplasms and Basal Cell Carcinoma: Baseline, Baseline-Followup Interval, and Lifetime Occurrence

Site	Statistic	Baseline[a]		Baseline-Followup Interval[b]		Lifetime Occurrence[b]	
All Malignant Skin Neoplasms	Number of Participants with Neoplasms/Percent:[c]						
	Ranch Hand	35	3.3%	37	3.9%	66	6.9%
	Comparison	25	2.0%	40	3.3%	66	5.4%
	Est. RR/p-Value	1.62	(0.07)[d]	1.18	(0.486)[e]	1.29	(0.175)[e]
	Adj. RR/p-Value	—*	—*	—*	—*	—*	—*
Basal Cell Carcinoma	Number of Participants with Neoplasms/Percent:[c]						
	Ranch Hand	31	3.0%	29	3.0%	53	5.5%
	Comparison	21	1.7%	30	2.5%	50	4.1%
	Est. RR/p-Value	1.71	(0.047)[d]	1.23	(0.429)[e]	1.36	(0.128)[e]
	Adj. RR/p-Value	—*	—*	****	****	1.56	(0.035)
All Malignant Systemic Neoplasms	Number of Participants with Neoplasms/Percent:[f]						
	Ranch Hand	13	1.2%	8	0.8%	17	1.7%
	Comparison	11	0.9%	7	0.5%	17	1.3%
	Est. RR/p-Value	1.35	(0.46)[d]	1.46	(0.603)[e]	1.28	(0.491)[e]
	Adj. RR/p-Value	—*	—*	1.51	(0.434)	****	****

—*Analysis not done

[a]Baseline participants: 1,045 Ranch Hands, 1,224 Comparisons.

[b]Followup participants: 1,016 Ranch Hands, 1,293 Comparisons.

[c]Nonblacks only for followup participants (956 Ranch Hands, 1,210 Comparisons), both nonblacks and Blacks for Baseline participants.

[d]Chi-square test.

[e]Fisher's exact test.

[f]All participants.

****Group-by-covariate interaction.

estimated lifetime relative risk appears closer to 1 than for the two intervals separately, but the small number of occurrences and intervening mortality preclude more definitive statements.

Baseline Participants

This brief section summarizes the mortality and malignant neoplasm history of the fully compliant Baseline participants in the interval up to the followup examination. Mortality information up through the end of 1985 was considered. This discussion is directed to the question of whether competing mortality affected the preceding analysis of incident cancers among living participants.

Of the 1,045 Ranch Hands and 1,224 Comparisons who were fully compliant at Baseline, 971 Ranch Hands and 1,139 Comparisons returned to the followup examination. Table 10-23 presents the numbers of Baseline participants according to whether they completed the followup examination and whether they were alive at the end of 1985.

TABLE 10-23.

Fully Compliant Baseline Participants by Status at Followup Examination and Group

Participated in Followup Examination	Status	Group		Total
		Ranch Hand	Comparison	
Yes	Dead[a]	3	2	5
	Alive	968	1,137	2,105
No	Dead	9	15	24
	Alive	65	70	135
Total		1,045	1,224	2,269

[a]Died in 1985, but subsequent to participation in the examination.

For the participants who did not return for the followup examination, Table 10-24 shows that 2 of the 9 deaths among Ranch Hands were due to malignant neoplasms, compared with 5 of the 15 deaths among the Comparisons. One Ranch Hand who died had a malignant skin neoplasm, but this was not the primary cause of death. Among the 65 Ranch Hands who did not return for the followup examination, 5 had verified malignant neoplasms at Baseline, including 1 systemic neoplasm (of the kidney), as contrasted with 2 among 70 Comparisons who had verified malignant (skin) neoplasms. Thus, among the 74 Ranch Hands not returning for followup, there were 8 with incident or fatal neoplasms, as compared to 7 of 85 Comparisons; the group difference was not significant ($p=0.788$).

TABLE 10-24.

Fully Compliant Baseline Participants
Who Did Not Participate in Followup Examination
by Status and Group

Status	Group		
	Ranch Hand	Comparison	Total
Dead--Primary Cause of Death:			
Malignant Neoplasm	2[a]	5[b]	7
Other Causes	7[c]	10	17
Lost to Followup:			
Verified Malignant Neoplasm at Baseline	5[d]	2[•]	7
No Malignant Neoplasm at Baseline	60	68	128

[a]Both with lung cancer.

[b]Three with lung cancer, one with malignant neoplasm of intestine (location unspecified), one with malignant neoplasm of an ill-defined site (face, head, or neck).

[c]Includes one Ranch Hand with malignant skin neoplasm.

[d]Four with malignant skin neoplasms, one with malignant systemic neoplasm (kidney).

[•]Two with malignant skin neoplasms.

For the participants who did return for the followup examination, Table 10-25 gives the frequencies and percentages of the respective group totals according to neoplasm status at Baseline and at followup. Analysis showed that there was no significant group difference (p=0.115) in the pattern of neoplasm incidence at Baseline and/or at followup.

The results of this section show approximate equivalence between the groups for the disease of cancer (fatal or nonfatal) since Baseline, and in the proportions of participants with malignancies at Baseline, followup, or both.

EXPOSURE INDEX ANALYSES

Unadjusted and adjusted exposure index analyses were conducted within each occupational cohort of the Ranch Hand group (see Chapter 8 for details on the exposure index). Interval and lifetime occurrences of basal cell carcinomas, sun-exposure related malignant skin neoplasms, and malignant systemic neoplasms were examined. As was done in the core analyses, verified conditions and verified plus suspected malignancies were each investigated. Blacks were excluded from all malignant skin neoplasm analyses. Group contrasts in incidence rates of malignant skin neoplasms were adjusted for the covariates of age, sun reaction index, and average residential latitude. Adjusted analyses for malignant systemic neoplasms accounted for the effects of age and race.

For each dependent variable, exposure level frequencies and percentages are presented in Appendix Tables H-26 and H-27, for interval and lifetime, respectively, along with the results of the unadjusted analyses. Pearson's chi-square test was used to reflect overall exposure index differences, and Fisher's exact test was used to investigate medium versus low and high versus low exposure level contrasts. Results of the adjusted analyses are presented in Tables 10-26 and 10-27, for interval and lifetime, respectively. These results are presented in the context of a main effects model containing exposure index and all adjusting covariates.

Several significant or marginally significant overall results were found. None was suggestive of a strictly increasing dose response effect; in fact, most showed decreasing incidence rates with increasing exposure.

Among officers, in the unadjusted interval analysis, significant or marginally significant results were found among nonblacks for verified and suspected basal cell carcinomas (overall p=0.042), sun-exposure related malignant skin neoplasms (verified: overall p=0.096, verified plus suspected: overall p=0.021), and among Blacks and nonblacks for verified plus suspected malignant systemic neoplasms (overall p=0.081). These findings were primarily due to higher percentages of malignancies in the medium exposure level than in the high or low categories for each variable (see Appendix Table H-26 for frequencies). The corresponding adjusted analyses were nonsignificant for basal cell carcinoma (overall p=0.156), verified sun-exposure malignancies (overall p=0.272), and systemic malignant neoplasms (overall p=0.109). The adjusted results were marginally significant for verified plus suspected sun-exposure malignancies (overall p=0.095).

TABLE 10-25.

Fully Compliant Baseline Participants Also in Followup Examination by Malignant Neoplasm Status

Malignant Neoplasm at Baseline	Malignant Neoplasm at Followup	Group				Total
		Ranch Hand		Comparison		
		Number	Percent	Number	Percent	
Yes	Yes	10	1.0	15	1.3	25
	No	37	3.8	28	2.5	65
No	Yes	36	3.7	31	2.7	67
	No	888[a]	91.5	1,065[a]	93.5	1,953
Total		971		1,139		2,110

[a]Includes three Ranch Hands and two Comparisons who died after followup.

TABLE 10-26.

Adjusted Exposure Index Analysis for Followup Participants for occurrence of Malignant Neoplasms in the Baseline-Followup Interval

Variable	Occupation	Exposure Index Low Total*	Exposure Index Medium Total*	Exposure Index High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	124	127	121	Overall		0.415
					M vs. L	2.02 (0.50,8.10)	0.320
					H vs. L	0.91 (0.18,4.68)	0.908
Basal Cell[a] Carcinoma (Verified Only)	Enlisted Flyer	54	61	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.346
					M vs. L	0.51 (0.07,3.53)	0.496
					H vs. L	0.19 (0.02,2.14)	0.179
	Officer	124	127	121	Overall		0.156
					M vs. L	2.40 (0.73,7.88)	0.149
					H vs. L	0.91 (0.22,3.76)	0.892
Basal Cell[a] Carcinoma (Verified and Suspected)	Enlisted Flyer	54	61	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.165
					M vs. L	0.36 (0.06,2.25)	0.274
					H vs. L	0.14 (0.01,1.44)	0.098

TABLE 10-26. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Occurrence of Malignant Neoplasms in the Baseline-Followup Interval

Variable	Occupation	Exposure Index Low Total*	Exposure Index Medium Total*	Exposure Index High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	124	127	121	Overall		0.272
					M vs. L	2.38 (0.61,9.30)	0.214
					H vs. L	0.95 (0.18,4.88)	0.949
Sun-Exposure[a] Related Malignancies (Verified Only)	Enlisted Flyer	54	61	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.767
					M vs. L	0.83 (0.15,4.55)	0.826
					H vs. L	0.50 (0.07,3.39)	0.481
	Officer	124	127	121	Overall		0.095
					M vs. L	2.68 (0.83,8.67)	0.100
					H vs. L	0.93 (0.22,3.86)	0.921
Sun-Exposure[a] Related Malignancies (Verified and Suspected)	Enlisted Flyer	54	60	51	Overall		0.080
					M vs. L	0.35 (0.05,2.20)	0.261
					H vs. L	0.11 (0.01,1.10)	0.061
	Enlisted Groundcrew	138	149	129	Overall		0.514
					M vs. L	0.59 (0.12,2.94)	0.519
					H vs. L	0.36 (0.06,2.20)	0.268

TABLE 10-26. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Occurrence of Malignant Neoplasms in the Baseline-Followup Interval

Variable	Occupation	Exposure Index Low Total*	Exposure Index Medium Total*	Exposure Index High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	127	130	123	Overall		0.365
					M vs. L	1.60 (0.15,17.22)	0.696
					H vs. L	--	--
Systemic[b] Malignancies (Verified Only)	Enlisted Flyer	55	65	57	Overall		--
					M vs. L	--	--
					H vs. L	--	--
	Enlisted Groundcrew	154	163	142	Overall		--
					M vs. L	--	--
					H vs. L	--	--
	Officer	127	130	123	Overall		0.109
					M vs. L	2.95 (0.31,27.73)	0.344
					H vs. L	--	--
Systemic[b] Malignancies (Verified and Suspected)	Enlisted Flyer	55	65	57	Overall		0.557
					M vs. L	0.25 (0.02,3.90)	0.326
					H vs. L	0.38 (0.03,4.90)	0.458
	Enlisted Groundcrew	154	163	142	Overall		--
					M vs. L	--	--
					H vs. L	--	--

*Total number of participants.
[a]Nonblacks only.
[b]Blacks and nonblacks.
--Analyses not done due to sparse cells.

TABLE 10-27.

Adjusted Exposure Index Analysis for Followup Participants for Lifetime Occurrence of Malignant Neoplasms

Variable	Occupation	Exposure Index Low Total*	Exposure Index Medium Total*	Exposure Index High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	124	127	121	Overall		0.841
					M vs. L	1.33 (0.48,3.66)	0.580
					H vs. L	1.27 (0.45,3.60)	0.647
Basal Cell Carcinoma (Verified Only)[a]	Enlisted Flyer	54	61	51	Overall		0.024
					M vs. L	0.23 (0.03,1.61)	0.141
					H vs. L	0.08 (0.01,0.78)	0.030
	Enlisted Groundcrew	138	149	129	Overall		0.937
					M vs. L	1.10 (0.31,3.86)	0.881
					H vs. L	0.87 (0.24,3.20)	0.832
	Officer	124	127	121	Overall		0.699
					M vs. L	1.49 (0.59,3.78)	0.404
					H vs. L	1.22 (0.46,3.24)	0.694
Basal Cell Carcinoma (Verified and Suspected)[a]	Enlisted Flyer	54	60	51	Overall		0.024
					M vs. L	0.23 (0.03,1.61)	0.141
					H vs. L	0.08 (0.01,0.78)	0.030
	Enlisted Groundcrew	138	149	129	Overall		0.860
					M vs. L	0.89 (0.27,2.97)	0.849
					H vs. L	0.71 (0.20,2.48)	0.589

TABLE 10-27. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Lifetime Occurrence of Malignant Neoplasms

Variable	Occupation	Exposure Index Low Total*	Medium Total*	High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
Sun-Exposure Related Malignancies (Verified Only)[a]	Officer	124	127	121	Overall		0.906
					M vs. L	1.19 (0.47,3.00)	0.717
					H vs. L	0.99 (0.37,2.64)	0.980
	Enlisted Flyer	54	61	51	Overall		0.045
					M vs. L	0.42 (0.08,2.19)	0.300
					H vs. L	0.09 (0.01,0.89)	0.039
	Enlisted Groundcrew	138	149	129	Overall		0.785
					M vs. L	1.35 (0.40,4.58)	0.627
					H vs. L	0.88 (0.24,3.25)	0.850
Sun-Exposure Related Malignancies (Verified and Suspected)[a]	Officer	124	127	121	Overall		0.722
					M vs. L	1.33 (0.56,3.16)	0.518
					H vs. L	0.97 (0.38,2.47)	0.952
	Enlisted Flyer	54	60	51	Overall		0.045
					M vs. L	0.42 (0.08,2.19)	0.300
					H vs. L	0.09 (0.01,0.89)	0.039
	Enlisted Groundcrew	138	149	129	Overall		0.785
					M vs. L	1.10 (0.34,3.52)	0.879
					H vs. L	0.72 (0.20,2.52)	0.603

TABLE 10-27. (continued)

Adjusted Exposure Index Analysis for Followup Participants for Lifetime Occurrence of Malignant Neoplasms

Variable	Occupation	Exposure Index Low Total*	Exposure Index Medium Total*	Exposure Index High Total*	Contrast	Adj. Relative Risk (95% C.I.)	p-Value
	Officer	127	130	123	Overall		0.902
					M vs. L	1.11 (0.18,7.01)	0.911
					H vs. L	1.49 (0.24,9.16)	0.669
Systemic Malignancies (Verified Only)[b]	Enlisted Flyer	55	65	57	Overall		0.806
					M vs. L	0.86 (0.11,7.08)	0.892
					H vs. L	0.46 (0.04,5.46)	0.540
	Enlisted Groundcrew	154	163	142	Overall		0.073
					M vs. L	--	--
					H vs. L	--	--
	Officer	127	130	123	Overall		0.829
					M vs. L	1.69 (0.30,9.65)	0.554
					H vs. L	1.47 (0.24,8.95)	0.679
Systemic Malignancies (Verified and Suspected)[b]	Enlisted Flyer	55	65	57	Overall		0.741
					M vs. L	0.51 (0.08,3.47)	0.494
					H vs. L	0.54 (0.08,3.57)	0.527
	Enlisted Groundcrew	154	163	142	Overall		0.087
					M vs. L	--	--
					H vs. L	--	--

*Total number of participants.
[a]Nonblacks only.
[b]Blacks and nonblacks.
--Analyses not done due to sparse cells.

For the interval analysis, enlisted flyers exhibited a marginally significant decreasing dose-response effect for verified basal cell carcinomas in both the unadjusted (p=0.073) and adjusted analyses (p=0.080). (All Ranch Hand enlisted flyer interval malignant skin neoplasms were verified basal cell carcinomas; thus, interval results for verified and verified plus suspected basal cell carcinoma and the corresponding sun-exposure related neoplasms were identical. Similarly, for lifetime analyses, verified and verified plus suspected analyses were the same). The percentages of participants with interval basal cell neoplasms were 11.1 percent, 3.3 percent, and 1.9 percent for the low, medium, and high exposure categories, respectively. The enlisted groundcrew exhibited a nonsignificant decreasing dose-response effect for basal cell carcinomas and sun-exposure related malignant neoplasms.

In the adjusted lifetime analysis for enlisted flyers (Table 10-27), there were significant findings, similar to the interval analysis, namely a decreasing dose-response effect for basal cell carcinomas (overall p=0.024; Adj. RR [medium versus low]: 0.23, 95% C.I.: [0.03, 1.61], Adj. RR [high versus low]: 0.08, 95% C.I.: [0.01, 0.78]), and for sun-exposure related skin malignancies (overall p=0.045; Adj. RR [medium versus low]: 0.42, 95% C.I.: [0.08, 2.19], Adj. RR [high versus low]: 0.09, 95% C.I.: [0.01, 0.89]). The percentages of participants with lifetime basal cell carcinomas were 13.0 percent, 3.3 percent, and 1.9 percent for the low, medium, and high exposure categories, respectively. The corresponding percentages for lifetime sun-exposure related skin malignancies were 13.0 percent, 4.9 percent, and 1.9 percent. For the enlisted groundcrew cohort, a marginally significant result was found for all systemic malignancies combined in the adjusted analyses (verified only: overall p=0.073; verified plus suspected: overall p=0.087). Of the four verified systemic malignancies, three were in the medium exposure category and one was from the high category. There was one additional suspected malignant neoplasm in the high exposure category. No significant results were found for officers in the lifetime analysis.

DISCUSSION

The statistical analyses of cancer endpoints in this chapter have carefully followed the prescribed boundaries of the SAIC analytic plan approved by the Air Force. Specific latency analyses of certain cancers associated with environmental exposures were not performed, nor were contrasts of cancer-specific incidence rates to SEER data judged appropriate. Further, embedded case control studies on selected cancers were not performed due to concern for bias.

The statistical analyses focused on neoplasms occurring during the time interval between 1982 and 1985 (Baseline to followup). However, because these relatively young and healthy cohorts yielded small numbers of cancers in this short interval, and because of the intense scientific interest in malignant disease, the analysis went beyond the assessment of the incidence of malignant neoplasms in this interval. Lifetime (Baseline and followup data combined) analyses of malignant incident neoplasms were conducted. Cancers occurring prior to military duty in SEA were excluded. A full cancer mortality-morbidity analysis was not attempted but simple tabulations of cancer incidence and mortality of Baseline participants were made. Interval and lifetime analyses were expanded to include suspected cancers noted at followup. Further, grouped cancers that were not likely related were

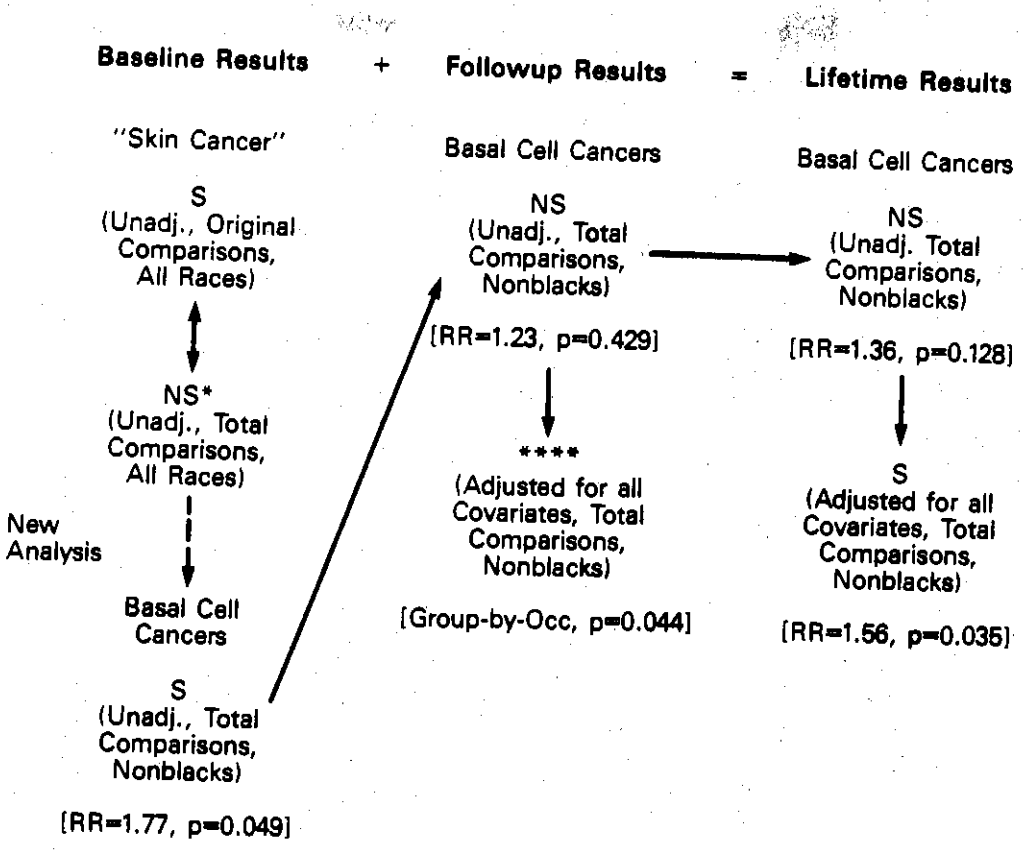
analyzed (all systemic cancers and malignant sun exposure-related skin neoplasms). These efforts, however, have introduced several subtle interpretive issues that should be noted, e.g., skin cancer rates are for nonblacks only, whereas systemic cancer rates are for all races; lifetime group rates are on only those attending the followup examination; and verified and suspected cancer categories included more cases but the data are less reliable. Further, contrasts of cancer rates, particularly skin cancer, between the Baseline results and followup results, or lifetime results, must account for the slight differences in the Baseline and followup cohorts, racial adjustment (Blacks were not omitted from skin cancer analyses at Baseline), skin cancer classification, the change in focus from the Original Comparisons to the total Comparison group, and whether the data were adjusted for covariates.

Skin Cancer

The emphasis on skin cancer at the followup examination was predicated upon the finding of a significant excess of such cancers at the Baseline examination, and the lack of risk factor data to conduct appropriate adjusted analyses. Because of shifting factors (cited above) between the examinations, a "direct look" at the skin cancer association is not straightforward. Figure 10-1 is presented as an aid to clarify the skin cancer observations over the two examinations.

This diagram compares the Baseline and followup analyses. So that the unadjusted Baseline results could be contrasted to the followup results, the estimated relative risk of basal cell carcinoma among nonblack Ranch Hands versus all nonblack Comparisons (not just Originals) was calculated, using data in the Baseline Report. This unadjusted analysis gave a significant relative risk of 1.77 (p=0.049). These results could then be directly contrasted to the unadjusted followup results, which showed a narrowing of group differences over the 3-year interval (Est. RR: 1.23, p=0.429). (It is noted that this contrast compares skin cancer rates of approximately 23 years to 3 years at different levels of age risk.) The adjusted analysis revealed a significant group-by-occupation interaction, due to a significantly higher rate of basal cell carcinomas among Ranch Hand enlisted flyers than the corresponding Comparisons (Adj. RR: 6.50, p=0.019), but very similar rates in the two groups for officers and enlisted groundcrew were seen.

The Baseline data were carefully merged (to avoid duplicate counts) with the followup data to assess the total lifetime incidence of basal cell carcinomas between groups. The addition of the nonsignificant followup results to the significant Baseline results produced a nonsignificant lifetime assessment (Est. RR: 1.36, p=0.128), as expected. However, when the lifetime data were adjusted for covariate effects, a significant result emerged (Adj. RR: 1.56, p=0.035), with Ranch Hands having a significant excess of lifetime basal cell carcinoma. A careful examination of the covariates showed that the variable of average residential lifetime latitude was most likely responsible for the significant adjusted results. The latitude variable was a significant confounding variable since it was associated with basal cell carcinomas and with average lifetime latitude which varied significantly by group.



S: Significant ($p \leq 0.05$).
NS: Not significant ($p > 0.10$).
NS*: Borderline significant ($0.05 < p \leq 0.10$).
****: Group-by-covariate interaction.

Figure 10-1.
Schematic Diagram of Unadjusted and Adjusted Skin Cancer Results, by Significance and Relative Risk, and by Examination Period (Time).

Because of the significant confounding effect of the latitude variable, it was examined closely for misclassification or bias. An initial review of the residential history forms showed occasional discrepancies between total residential years and chronologic age. This was generally due to sporadic underreporting, and to the data collection instructions which required the citation only of residences of one year or longer. However, analyses showed fairly good concordance between reported residential years and chronologic age. No significant group difference was found for the inaccuracy of residential reporting ($p=0.684$), validating the use of all residential histories even though some were slightly imprecise.

In the course of reviewing the covariate effects on basal cell carcinoma, the data suggested some unexpected associations. To sharpen these contrasts, adjusted risks were estimated at set levels of skin reaction to sun, skin color, average lifetime residential latitude, and age, relative to the lowest risk observed, i.e., Comparisons 40 years old (at Baseline) who have lived on average in northern latitudes and tan easily were arbitrarily assigned a risk of 1.00. These computed risks are given in Table 10-28.

These results show uniform increased risks in the Ranch Hands over both the base level of one and the Comparisons in the same covariate strata. Further, in all strata, age, latitude, and skin color behave as expected. However, the sun-reaction index does not behave as expected since those who burn easily have lower relative risks than those who have an intermediate reaction to sun, although they do have higher relative risks than those who tan easily. This may represent avoidance of sun exposure or the use of sunblock by those individuals.

Skin cancer, and particularly basal cell carcinoma, has been emphasized in this report because of the significant group differences detected at Baseline (and the theoretical link to TCDD causation), and the borderline significant adjusted results found for the lifetime rates. The results of the third-year followup analysis suggest that if group differences continue to narrow (where $p \geq 0.15$) at the fifth-year followup examination, the lifetime results would likely not be significant even with full adjustment.

Systemic Cancer

The analyses of systemic cancer for both the interval and lifetime periods have necessarily been limited by scant data. Cancer specific analyses, in particular, have not provided meaningful results because of low counts. However, some variation in tumor type was noted in the two groups: colon cancer (5 Comparisons, 0 Ranch Hands), testicular cancer (3 Ranch Hands, 0 Comparisons), and smoking related tumors of the oral cavity, pharynx, bronchus, and lung (5 Ranch Hands, 0 Comparisons). Testicular and smoking related tumors have not been associated with exposure to herbicides or TCDD. Table 10-18 cited counts of malignancies that have been associated to herbicides and dioxin exposure. Because of the relative rareness of the diseases soft tissue sarcoma (STS), Hodgkin's disease, and non-Hodgkin's lymphoma, lifetime rates were expected to be exceptionally low.

Most of the covariate associations with systemic cancer were anticipated, but the change in significance for smoking (significant at Baseline, borderline significant for lifetime cancers) was not expected, particularly as the cancer cases increased during the interval.

TABLE 10-28.

Computed Risks of Basal Cell Carcinoma by Group at Varying Levels of Four Risk Factors, Relative to Comparisons at Low Risk*

Covariate Categories			Skin Color: Not Peach		Skin Color: Peach	
Skin Reaction to Sun	Average Lifetime Residential Latitude	Age at Baseline	Comparison	Ranch Hand	Comparison	Ranch Hand
Tans Easily	≥37°N	40	1.00**	1.48	1.55	2.30
		60	2.99	4.43	4.62	6.85
	<37°N	40	1.63	2.42	2.52	3.74
		60	4.87	7.23	7.53	11.18
Intermediate Reaction	≥37°N	40	3.04	4.52	4.71	6.99
		60	9.09	13.50	14.06	20.87
	<37°N	40	4.97	7.37	7.68	11.40
		60	14.83	22.02	22.93	34.04
Burns Easily	≥37°N	40	2.02	3.00	3.13	4.64
		60	6.04	8.96	9.33	13.86
	<37°N	40	3.30	4.90	5.10	7.57
		60	9.85	14.62	15.22	22.60

*Computed from main effects model with latitude, skin reaction to sun, and skin color as covariates.

**Base Category (Lowest Risk).

All Cancers

As previously noted, the interrelatedness of many of the analyzed cancer variables has created a compounding of statistical significance, and care should be taken in making inferences and final conclusions. An almost uniform dilutional effect was created by adding "suspected" cancers to the analyses, as there were more of this category in the Comparisons than in the Ranch Hands. The use of suspected neoplasms was deemed necessary in order to best describe the complete cancer findings, recognizing that confirmation of all suspected cases was difficult.

Two patterns emerged from the analyses. All relative risks exceeded the value of one, except that of lifetime verified melanoma and verified or verified plus suspected squamous cell carcinoma. Some of the elevated risks were due to the relatedness of the variables as stated, but the relative risks for the unrelated variables skin cancer and systemic cancer both exceeded one. The joint consideration of both yielded a significant relative risk. The second pattern was of the group-by-covariate interactions observed for seven of the analyses; 3 of them involved the covariate of occupation and 4 involved skin reaction to sun. The three group-by-occupation interactions all showed a significant detriment to the Ranch Hand enlisted flying cohort. Further analyses of air crewmembers versus noncrewmembers revealed a significant risk of basal cell carcinoma for the Ranch Hand air crewmembers (RR: 1.94, $p=0.049$). Since enlisted Ranch Hand flyers in the interval exhibited more basal cell carcinomas (RR: 6.5, $p=0.019$) and more verified and suspected systemic cancers (4/175 RH with systemic neoplasms versus 0/209 Comparisons, $p=0.042$), there may be more reason to assume a biologic foundation than chance, although the reason is obscure. The four group-by-sun reaction index interactions all revealed a significant or marginally significant detriment to Ranch Hands who reacted mildly to the sun.

In full context, the cancer observations cannot be viewed as disturbing at this time. The skin cancer group differences have narrowed over a 3-year period. An additional analytic observation on skin cancer is that inclusion or exclusion of only one or two cases was shown to alter the choice of the best statistical model, affecting the presence or absence of both covariates and group-by-covariate interactions, and also change the p-value of the adjusted group difference above or below the alpha level of 0.05. For systemic cancer, both groups are at the lower end of the expected ascending cancer curves, where numeric and tumor type fluctuations are expected. A recognized bench-mark for the latency of many cancers is 20 years, and this will not be achieved by most participants until the 5-year followup examination, 2 years from now. Cancer findings at that time will be the basis upon which firm conclusions can be made.

SUMMARY AND CONCLUSIONS

The cancer analysis focused on cancer occurrences in the Baseline-followup interval, and also included analyses of the Baseline plus interval cancer history. A summary of the cancer findings is given in Table 10-29.

No significant unadjusted differences were found between nonblack Ranch Hands and Comparisons in the Interval (Baseline-Followup) incidence rates of basal cell carcinoma, melanoma, squamous cell carcinoma, all malignant skin cancers, sun-exposure related malignant neoplasms (comprising basal cell

TABLE 10-29.

Overall Summary Table: Unadjusted and Adjusted Analysis of Interval and Lifetime Skin and Systemic Cancer Incidence

Cancer Type	Baseline-Followup Interval		Lifetime (Baseline & Followup)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Malignant Skin Cancer (Nonblacks only)				
Verified Basal Cell Carcinoma	NS	****	NS	S
Verified plus Suspected Basal Cell Carcinoma	NS	****	NS	****
Verified Melanoma	NS	--[a]	NS	--[a]
Verified plus Suspected Melanoma	NS	--[a]	NS	--[a]
Verified Squamous Cell Carcinoma	NS	--[a]	NS	--[a]
Verified plus Suspected Squamous Cell Carcinoma	NS	--[a]	NS	--[a]
Verified Sun Exposure Skin Cancers	NS	NS	NS*	S
Verified plus Suspected Sun Exposure Skin Cancers	NS	NS	NS	NS
All Verified Malignant Skin Cancers	NS	--[a]	NS	--[a]
Verified plus Suspected Malignant Skin Cancers	NS	--[a]	NS	--[a]
Verified Skin Cancers of Any Type	NS*	--	S	--
Verified plus Suspected Skin Cancers of Any Type	NS	--	NS*	--

TABLE 10-29.

Overall Summary Table: Unadjusted and Adjusted Analysis of Interval and Lifetime Skin and Systemic Cancer Incidence (continued)

Cancer Type	Baseline-Followup Interval		Lifetime (Baseline & Followup)	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Malignant Systemic Cancer (Blacks and Nonblacks)				
Verified Systemic Cancer	NS	NS	NS	****
Verified plus Suspected Systemic Cancer	NS	****	NS	****
All Neoplasms (Blacks and Nonblacks)				
Any Type, Any Location[b] Verified	NS*	--[a]	S	--[a]

NS: Not significant ($p>0.10$).

****Group-by-covariate Interaction.

--[a]Analysis not done.

NS*: Borderline significant ($0.05<p\leq0.10$).

[b]Comprises malignant, benign, uncertain behavior.

S: Significant ($p\leq0.05$).

carcinoma, melanoma, and epithelial neoplasms NOS) or all malignant skin cancers as a group. The unadjusted group contrast of all skin neoplasms (comprising malignant and benign neoplasms, and neoplasms of uncertain behavior or unspecified nature) was marginally significant, with a higher rate among Ranch Hands. When suspected malignant skin cancers (noted at Followup but not verified at the time of writing) were included in the analyses with the verified conditions, all the unadjusted group contrasts were nonsignificant.

The covariates used for the adjusted analyses of basal cell carcinoma and the sun exposure related skin malignancies were age, occupation, skin color, reaction of skin to sun, and average latitude, all of which were highly associated with skin cancer incidence. Other host factors were related to skin cancer incidence, but not as strongly as those included in the analysis. A borderline association with smoking history was noted, and was determined to be partly an age effect.

Analysis of the incidence of interval basal cell carcinoma revealed a significant group-by-occupation interaction, due to a significant group difference for enlisted flyers, but not for officers or enlisted groundcrew. Inclusion of suspected basal cell carcinoma resulted in a group-by-sun reaction index interaction. This was due to Ranch Hands with an intermediate reaction to sun having a higher relative risk than the corresponding Comparisons. The adjusted group contrast of the incidence rates of verified sun-exposure related skin cancers was not significant; inclusion of suspected conditions did not alter this lack of significance.

There was no significant group difference for Blacks and nonblacks in the unadjusted incidence rates of all interval verified malignant systemic neoplasms combined, nor was there a significant difference in the adjusted group rates. Analysis of the verified plus suspected interval systemic cancers showed a nonsignificant unadjusted group difference, but a group by occupation interaction was found in the adjusted analysis. This was due to a significant group difference of verified plus suspected systemic malignancies among the enlisted flyers with five occurrences among the Ranch Hands, but none among the Comparisons. Age and a race-by-packyear interaction were important adjusting factors.

The Baseline and Followup data were combined for the assessment of lifetime incidence of cancer; occurrences of cancer prior to Vietnam were excluded.

There were no significant unadjusted group differences in lifetime incidence rates among nonblacks for basal cell carcinoma, melanoma, squamous cell carcinoma, the sun exposure related skin cancers, or all malignant skin cancers combined. The unadjusted group contrast of all lifetime skin malignancies was significant, with a higher rate among Ranch Hands. Inclusion of suspected cancers with the verified cancers reduced the difference between the groups for all these malignant skin contrasts, except for the sun exposure related skin cancers, for which a marginally significant group difference was found. However, the contrast of all skin malignancies remained close to significance.

Adjusted analysis of the incidence rates of lifetime basal cell carcinoma revealed a significantly higher incidence rate among Ranch Hands

(Adj. RR: 1.56, p=0.035). Significant effects of an occupation-by-age interaction, a skin color-by-sun reaction index interaction, and a sun reaction index-by-average residential latitude interaction were seen. The adjustment resulted in a significant relative risk that, moreover, was higher than the unadjusted relative risk. Average residential latitude, associated with both group and skin cancer, and skin color, which was associated with the disease and marginally associated with group, played a major part in the change from the unadjusted analysis due to confounding. Inclusion of suspected basal cell carcinoma in the adjusted analysis resulted in a group by sun reaction index interaction, as was noted for the interval analysis.

The adjusted group contrast in incidence rates of the sun-exposure related skin cancers was also significant (Adj. RR: 1.54, p=0.030), which is not surprising since the majority are basal cell carcinoma. Inclusion of the suspected conditions resulted in a non-significant group contrast.

The unadjusted group contrasts of the incidence rates of all systemic cancers combined were not significant, both for verified and verified plus supected conditions.

There was one new occurrence of a soft tissue sarcoma (Ranch Hand) and one suspected cancer of the lymphatic system (Ranch Hand), in addition to the one previously reported soft tissue sarcoma and one Hodgkin's disease in the Comparison group.

Adjusted analysis of all lifetime malignant systemic neoplasms as a group, however, revealed a group by occupation interaction, due to a significantly higher rate for Ranch Hand enlisted flyers as contrasted to Comparisons. The same result was found for verified plus suspected systemic cancers.

In conclusion, there were no adjusted or unadjusted differences between groups in basal cell carcinoma incidence in the Baseline-followup interval. At Baseline, a significantly higher rate of basal cell carcinoma was found for Ranch Hands when contrasted with Original Comparisons. When the Baseline data were combined with the interval data, adjusted analysis, but not the unadjusted analysis, revealed a significantly higher rate of basal cell carcinoma among the Ranch Hands than among all Comparisons. The relative risk of basal cell carcinoma appears to be declining over time.

Relative risks of basal cell carcinoma and systemic cancer were found to be consistently larger than 1. Most of the skin cancers were basal cell carcinomas, upon which most of the skin cancer analysis focused, thus relative risks for sun-exposure related skin neoplasms and all malignant skin cancers as a group were very similar to those for basal cell carcinoma. The number of occurrences of systemic cancer was small, in part because the cohort is relatively young, and although the relative risks (lifetime and interval) are greater than 1, the difference between groups is not significant. Sufficient time may not have elapsed since Vietnam to enable a group difference in systemic neoplasms, if one exists, to be apparent.

CHAPTER 10

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CHAPTER 11

NEUROLOGICAL ASSESSMENT

INTRODUCTION

Neurological signs and symptoms, as distinguished from overt diagnosable neurological disease, have been consistently associated with industrial exposure to chlorophenols, phenoxy herbicides, and TCDD. Thus, the neurological system comprises a major examination focal point in all dioxin morbidity studies. This report carefully separates central and peripheral neurological status from "neurobehavioral" parameters, which are discussed in Chapter 12, Psychological Assessment.

Based on animal experiments, neurotoxicity can be attributed to the compounds 2,4-D and TCDD. For low to moderate doses, both central and peripheral acute effects occur but appear to be reversible.[1-3] The effects of 2,4-D are presumably due to disruption in the neuromuscular transport system of organic acid anions.[4] A variety of 2,4-D experiments in several animal species generally shows a wide range of neural pathology including electroencephalographic (EEG) desynchronization, demyelination, myotonia, loss of coordination, and uncontrolled motor activity. No substantive data support the isolated neurotoxicity of 2,4,5-T.

Numerous case reports following accidental human exposures or suicide attempts with 2,4-D have shown a remarkable neurologic parallel to the animal studies.[5-16] In particular, 2,4-D and TCDD have been implicated in a wide array of central neurological signs and symptoms, including headache, vomiting, dizziness, disorientation, sleep disturbance, stupor, memory loss, loss of coordination, and EEG abnormalities or alterations from a baseline tracing.[5-7,9,11-13] Peripheral abnormalities have included demyelination, acute degeneration of ganglion cells, temporary paralysis, anesthesia, hyperesthesia, paresthesia, neuralgic pain, numbness, tingling, muscle pain, muscle fasciculations, depressed or absent deep tendon reflexes, weakness, decreased nerve conduction velocities, "polyneuritis," and limb fatigue.[5-16] These peripheral signs and symptoms in industrial workers have received the generic diagnostic label "neurasthenia." Both the number and severity of symptoms tended to aggregate in individuals with chloracne as contrasted to those without chloracne.[11,16,17]

In general, there is consistency between the various case reports of neurasthenia and results from uncontrolled clinical studies. Of particular relevance is the consistency in findings from studies of both industrial manufacturing and industrial accidents. This literature provides the clear-cut conclusion that neurological impairment is caused directly by exposure to 2,4-D and TCDD. Not answered satisfactorily in the literature, however, are the issues of complete reversibilty of observed signs and symptoms and the long-term impact on health and quality of life.

Because of the conclusive evidence that two of three Agent Orange ingredients cause neurological "disease," it follows that significant exposure to Agent Orange could manifest neurologic signs, symptoms, or sequelae. In fact, over 10 percent of Vietnam veterans who enlisted in the VA Agent Orange Registry cited one or more symptoms of the neurasthenic complex.[18]

The VA Registry is a comprehensive listing, predominantly of veterans alleging health impairments due to Agent Orange exposure. The Registry does not purport to be a scientific effort upon which cause-and-effect relationships can be established. Nonetheless, some individuals believe that the symptom array in the VA Registry is so compatible with case reports and numerator-oriented clinical studies that the veterans must, in fact, have suffered adverse health effects from their Vietnam service and presumed exposure to Agent Orange. Others point to the intense media attention to "Agent Orange symptoms" during the formation of the Registry, and presume that the veterans' complaints are largely due to an "over-reporting" or compensation bias.

Clearly, only well-controlled, well-conducted epidemiologic studies of veterans known to have been exposed to Agent Orange can answer the question of cause and effect for illnesses, including the specific question of whether single or multiple neurologic signs and symptoms are also attributable to these exposures.

Baseline Summary Results

The 1982 AFHS neurological assessment consisted of questionnaire, physical examination, and electromyographic data obtained by examiners and technicians who were blinded to the group identity of each participant. The physical examination required an average of 30 minutes to complete. Those few individuals with positive RPR tests, a screening serological test for syphilis, and those with peripheral edema were deleted from the statistical analyses. Covariates of reported alcohol usage, exposure to insecticides and industrial chemicals, and glucose intolerance (diabetes) were analyzed. 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 all 12 cranial nerves, nor any effects due to the covariates of alcohol or diabetes. Peripheral nerve function was assessed by the quality of four reflexes (patellar, Achilles, biceps, and Babinski), muscle strength/bulk, and reaction to the stimuli of pin prick, light touch, and vibration. Other than a statistically significant increase ($p=0.03$) in Ranch Hand Babinski reflexes, significant group differences were not detected. The alcohol covariate demonstrated a marginal effect ($p=0.07$) on pin-prick reaction, while glucose intolerance showed a profound effect on the patellar and Achilles reflexes and reactions to light touch and vibration.

Nerve conduction velocities were obtained on the ulnar nerve, above and below the elbow, and the peroneal nerve by highly standardized methods. The results for each segmental measurement were nearly identical in the Ranch Hand and Comparison groups. Conduction velocity showed highly significant inverse relationships to both alcohol (measured in drink-years) and glucose intolerance in almost all of the anatomic measurements. No group associations or interactions were detected with the covariates of 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's 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.

Of a total of 84 exposure index analyses on all of the dependent variables, 3 were statistically significant but were either nonlinear or biologically implausible. In summary, the detailed neurological examination and assessment did not reveal statistically significant increases in abnormalities in the Ranch Hands, nor were consistent dose-response relationships noted for herbicide exposure. The classical neurological effects of alcohol ingestion and diabetes were repeatedly observed in the neurological evaluations.

Parameters of the 1985 Neurological Assessment

The 1985 AFHS neurological examination deleted the measurements of nerve conduction velocities but otherwise repeated the format of the Baseline examination. The questionnaire maintained a historical focus of neurasthenia via five questions for the 1982-1985 interval.

With this similarity in examination and questionnaire, the dependent variables of the analyses were almost identical to those of the Baseline study, however, the number of covariates was slightly increased. Diabetic status was trichotomized: Individuals reporting a history of diabetes (unverified) and individuals exhibiting glucose intolerance with postprandial glucose levels greater than or equal to 200 mg/dl were classified as diabetic, participants with glucose levels of at least 140 mg/dl but less than 200 mg/dl were classified as impaired, and participants with glucose levels less than 140 mg/dl were classified as normal. Race was included as a covariate, and lifetime alcohol use was updated on the basis of enhanced information from the 1985 questionnaire.

The analyses were based on 1,016 Ranch Hands and 1,293 Comparisons. Individuals confirmed to be positive for syphilis by fluorescent treponemal antibody (FTA) testing were excluded from all analyses. Individuals with peripheral pitting or nonpitting edema were excluded only for the analyses of pin prick, light touch, and vibration. Numeric differences in the following tables are due to missing dependent variables or covariate data. The exclusions and missing covariate data are summarized in Table 11-1. The unadjusted analyses used chi-square or Fisher's exact test for frequency table analyses. Adjusted analyses were not performed where only sparse numbers of abnormalities were found. Logistic regression models were used in all adjusted analyses. Parallel analyses using Original Comparisons can be found in Appendix I, Tables I-3 through I-13.

RESULTS AND DISCUSSION

General

Detailed neurological data were obtained on all participants by standard physical examination techniques. Four board-certified SCRF neurologists, all

TABLE 11-1.

Exclusions and Missing Data
for Neurological Assessment by Group

Data Category	Group		
	Ranch Hand	Comparison	Total
Lifetime Alcohol History (Drink-Years); Missing Data	39	40	79
Peripheral Edema (Exclusion Category for Pin Prick, Light Touch, and Ankle Vibration)	13	16	29
Diabetic Class (Missing Data)	0	4	4
Positive Syphilis Serology (RPR and FTA) Exclusion Category	0	1	1

blinded to the exposure status of the participants, conducted the examinations. Data were collected to assess three specific clinical areas: cranial nerve function, peripheral nerve function, and central nervous system (CNS) function. The analyses in this chapter are presented in the order of these functional areas.

The unadjusted statistical analyses presented in this chapter are straightforward group contrasts of dichotomous (normal/abnormal) dependent variables using Fisher's exact test. Logistic regression models for adjusted analyses used the covariates of age (born in or after 1942, born between 1923 and 1941, born in or before 1922), race (Black, nonblack), occupation (OCC) (officer, enlisted flyer, enlisted groundcrew), diabetic class (DIAB) (normal, less than 140 mg/dl glucose; impaired, at least 140 mg/dl but less than 200 mg/dl glucose; diabetic, greater than or equal to 200 mg/dl glucose or past diabetic history), lifetime alcohol use (DRKYR) (total drink-years: 0, greater than 0 to 50, greater than 50), and unprotected exposure to insecticides (INS) (recorded as yes/no, excluding herbicide exposure). The models are "best-fit" following a step-down strategy beginning with all two-way interactions among the six covariates. Only variables with a substantial number of abnormalities were analyzed. Several summary indices were constructed for functionally related variables with low counts of abnormalities. A summary index was created for the cranial nerve function by combining the 15 cranial nerve parameters into a single index, which was classified as normal if all parameters were normal. Another cranial nerve function was created in a similar fashion, excluding neck range of motion due to the much higher percentage of abnormalities found for this variable relative to the other parameters. The four coordination parameters of the central nervous

system were similarly combined to form a summary index. These constructed indices are presented more for the purpose of inspection than for inference making. Since the corneal reflex (as one measure of the trigeminal nerve function) contained no abnormalities for either group, no table is presented with this variable.

The statistical power to detect a given relative risk in many of the subsequent analyses was somewhat limited. With the use of a two-sided α-level of 0.05 and power of 0.80, the sample sizes were sufficient to detect a 49 percent increase in the frequency of abnormal values for neck range of motion, a 69 percent increase for light touch but only a doubling for tremor, and an elevenfold increase for gag reflex. Power was generally poor in these analyses because of the extremely small number of abnormalities observed in both the Ranch Hand and Comparison groups.

Questionnaire Data

For the interval questionnaire, each participant was asked to update his health history for neurologic conditions occurring between 1982 and 1985. All affirmative histories were subjected to medical record verification, and appropriate ICD-9-CM coding. All verified neurological diseases were placed into six broad disease categories. These data are summarized in Table 11-2.

TABLE 11-2.

Unadjusted Analysis for Verified Neurological Disease by Group*--1982-1985

	Group Abnormalities					
	Ranch Hand		Comparison			
Disease Category	Number	Percent	Number	Percent	Total	p-Value**
Inflammatory Diseases	0	0.0	0	0.0	0	--
Hereditary and Degenerative Diseases	2	0.2	0	0.0	2	0.194
Peripheral Disorders	18	1.8	27	2.1	45	0.651
Disorders of the Eye	5	0.5	7	0.5	12	0.999
Disorders of the Ear	6	0.6	7	0.5	13	0.999
Other Disorders	8	0.8	3	0.2	11	0.069

*Based on 1,016 Ranch Hands and 1,293 Comparisons; some participants may be classified in more than one category.

**Fisher's exact test.

All of these analyses were based on very small numbers of abnormalities, but none of the six general disease categories showed statistically significant differences between groups, although the marginal significance of the Other Disorders category is of interest.

To determine whether lifetime differences in neurologic disease exist between the Ranch Hand and Comparison groups, verified followup data were combined with verified Baseline historical data. This tabulation is presented in Table 11-3.

TABLE 11-3.

Unadjusted Analysis for Verified Neurological Disease by Group*--Baseline and First Followup Studies Combined

	Group Abnormalities					
	Ranch Hands		Comparisons			
Disease Category	Number	Percent	Number	Percent	Total	p-Value**
Inflammatory Diseases	3	0.3	2	0.2	5	0.660
Hereditary and Degenerative Diseases	2	0.2	3	0.2	5	0.999
Peripheral Disorders	23	2.3	38	2.9	61	0.361
Disorders of the Eye	16	1.6	23	1.8	39	0.747
Disorders of the Ear	24	2.4	29	2.2	53	0.889
Other Disorders	15	1.5	14	1.1	29	0.453

*Based on 1,016 Ranch Hands and 1,293 Comparisons; some participants may be classified in more than one category.

**Fisher's exact test.

Like the followup data, the combined data revealed no statistically significant differences in any disease category. Also, there was no significant difference in patterns of disease for each group (p=0.721).

Physical Examination Data

Dependent Variable and Covariate Relationships: Cranial Nerve Function, Peripheral Nerve Status, and Central Nervous System Coordination

Responses from both groups were combined and analyzed with the six covariates. In addition, current drinking (yes/no) and lifetime history of

unprotected exposure to industrial and degreasing chemicals (yes/no) were also evaluated. Indices constructed from dependent variables from the cranial nerve function and central nervous system coordination processes were also included. A summary tabulation of covariate associations is shown in Table 11-4. The 10 variables in this table include variables from the peripheral nerve status and CNS process as well as the cranial nerve function and constitute the subset of variables for which adjusted analyses were performed.

These results generally showed the profound association of classical risk factors for neurological deficits. Increases in the percentages of abnormalities for Achilles reflex, muscle status, neck range of motion, and the cranial nerve function index (which included neck range of motion) were associated with increases in age. Increasing percentages of abnormalities for pin prick and light touch were noted for increasing age from the young category (3.4% and 2.7% for pin prick and light touch, respectively) to the middle-aged category (8.1% and 4.7%, respectively), but a declining proportion of abnormalities was observed from the middle- to older-age categories (7.3% and 1.2%, respectively). No age effect was noted for gait, the CNS index, the cranial nerve index (neck range of motion excluded), and, surprisingly, for tremor.

Race was not a significant covariate for any dependent variable. A significant occupational effect was observed for the CNS summary index ($p=0.021$, with both enlisted categories having a higher frequency of abnormalities [5.7% and 4.1% for enlisted flyers and enlisted groundcrew, respectively] than the officer category [2.6%]) and for the neck range of motion variable ($p=0.010$, with increasing proportions of abnormalities from the enlisted groundcrew [4.6%] to officers [7.5%] to enlisted flyers[8.0%]).

Abnormalities in the Achilles tendon reflex were related to a graduated increase in drink-years of alcohol. For the variables of pin prick, light touch, muscle status, neck range of motion, and cranial nerve index (with neck range of motion included), the 0 drink-year category was related to a higher frequency of abnormalities than the greater than 0 to 50 drink-year category, which in turn was associated with a lower frequency of abnormalities than the greater than 50 drink-year category. For the current drinker (which was not used for modeling), the percentage of abnormalities for Achilles reflex and gait was significantly greater ($p=0.007$ and $p=0.001$ for Achilles reflex and gait, respectively) for current nondrinkers than for current drinkers. This relationship was reversed for the CNS summary index.

For both the Achilles tendon reflex and the response to pin prick, the frequencies of abnormalities significantly increased from the diabetic classes of normal to impaired to diabetic ($p<0.001$ for both variables). For the variables of light touch, muscle status, gait, and CNS summary index, the associations with diabetic status were mixed: The normal diabetic class had a higher proportion of abnormalities than the impaired stratum which, in turn, had a lower proportion of abnormalities than the overtly diabetic class. Unexpectedly, the proportion of tremor abnormalities was highest for the normal diabetic class and became successively lower in the impaired and diabetic strata (2.48%, 0.45%, and 0%, respectively).

A higher proportion of pin prick abnormalities was associated with a history of unprotected exposure to insecticides ($p=0.040$; 6.94% for exposed versus 4.8% for unexposed). The other dependent variables were not

TABLE 11-4.

Association Between Seven Neurological Variables and
Three Summary Indices and the Covariates in the Combined Ranch Hand and Comparison Groups

Dependent Variable	Covariate						Exposure		
	Age	Race	Occupation	Total Drink-years	Current Drinking*	Diabetic Class	Insecticides	Industrial Chemicals*	Degreasing Chemicals*
Achilles Reflex	<0.001	NS	NS	0.022	0.007	<0.001	NS	0.050	NS
Pin Prick	<0.001	NS	NS	0.004	NS	<0.001	0.040	NS	NS
Light Touch	0.027	NS	NS	0.006	NS	0.026	NS**	NS	NS
Muscle Status	<0.001	NS	NS	0.001	NS**	<0.001	NS	0.025	NS**
Gait	NS	NS	NS	NS	0.001	0.033	NS	NS	NS
CNS Index	NS	NS	0.021	NS	0.012	0.016	NS	NS	NS
Tremor	NS	NS	NS	NS	NS	0.011	NS	NS	NS
Neck Range of Motion	<0.001	NS	0.010	0.014	NS	NS**	NS	0.039	NS
Cranial Nerve Function Index	<0.001	NS	NS**	0.032	NS	NS	NS	NS**	NS
Cranial Nerve Function Index (Neck Range of Motion Excluded)	NS	NS	NS	NS**	NS	NS	NS	NS	NS

NS: Not significant ($p>0.10$).

* Variable not used in adjusted analyses.

NS**: Borderline significant ($0.05 < p \leq 0.10$).

significantly affected by the insecticide covariate. For most dependent variables, both Ranch Hands and Comparisons exposed to degreasing or industrial chemicals exhibited a smaller percentage of abnormalities than participants without exposure. Because the biologic basis of these findings is not readily apparent, these two variables were not used as adjusting covariates.

Cranial Nerve Function

All 12 cranial nerves were assessed as unilateral or bilateral; these unadjusted data are presented in Table 11-5. All bilateral assessments (e.g., right visual field, left visual field) were combined for the analyses; an abnormality consisted of a right and/or a left abnormality.

The analysis of the 12 variables and two cranial nerve function summary indices did not reveal statistically significant group differences. Since no abnormalities are present for the variables of speech and tongue position in the Comparison group, the estimated relative risk for these variables was approximated by adding 0.5 to each cell. The low frequency of abnormal counts in all variables, except neck range of motion, contrasts with the 1982 Baseline findings, which found substantially more abnormalities. For example, ocular movement was recorded as abnormal in more than 30 percent of the participants at Baseline while only 0.7 percent of participants were found to be abnormal at followup.

Because of the few abnormalities for all variables except neck range of motion, two summary indices of cranial nerve function were constructed. One indicated whether or not a participant is abnormal for any of the 15 variables, while the other was a composite for all except neck range of motion. The analyses of these indices are reflected in Table 11-5, and showed no statistically significant group differences, although the index excluding neck range of motion is of borderline significance. Speech and tongue position relative to midline were also of borderline significance, although the analysis was affected by sparse numbers of abnormalities. The constructed indices are presented more for the purpose of inspection than for inference making.

Because of sparse numbers of abnormalities, adjusted analyses were performed only on the variable neck range of motion and the cranial nerve function summary indices, with and without neck range of motion data. The results of these analyses are given in Table 11-6.

None of the results were statistically significant, although the cranial nerve function index, without neck range of motion, was marginally significant ($p=0.061$) when participants with missing drink-years were included. In the primary adjusted analysis for this variable, drink-years was included in a significant covariate interaction. However, an alternative model was also examined that included participants with missing drink-years due to the disparity in group response for these participants (4 out of 39 Ranch Hands abnormal, 0 out of 40 Comparisons abnormal). The results of these adjusted analyses are nearly identical to the unadjusted analyses (see Table 11-5). A borderline significant result of a group (GRP)-by-age interaction ($p=0.0501$) for neck range of motion existed, and an additional analysis stratifying by age is provided in Table 11-7. This table presents the results of interaction analyses from variables assessing the peripheral nerve status and central nervous system coordination process as well.

TABLE 11-5.

Unadjusted Analyses for Cranial Nerve Function by Group

Variable	Cranial Nerve	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Smell	I Olfactory	n	1,016		1,292			
		Abnormal	10	1.0	10	0.8	1.27 (0.53,3.07)	0.654
		Normal	1,006	99.0	1,282	99.2		
Visual Fields	II Optic	n	1,016		1,292			
		Abnormal	6	0.6	6	0.5	1.27 (0.41,3.96)	0.774
		Normal	1,010	99.4	1,286	99.5		
Light Reaction	III Oculomotor	n	1,015		1,289			
		Abnormal	8	0.8	9	0.7	1.13 (0.43,2.94)	0.811
		Normal	1,007	99.2	1,280	99.3		
Ocular Movements	III Oculomotor IV Trochlear VI Abducens	n	1,016		1,292			
		Abnormal	6	0.6	10	0.8	0.76 (0.28,2.10)	0.801
		Normal	1,010	99.4	1,282	99.2		
Facial Sensation	V Trigeminal	n	1,014		1,290			
		Abnormal	4	0.4	2	0.2	2.55 (0.47,13.95)	0.415
		Normal	1,010	99.6	1,288	99.8		
Jaw Clench	V Trigeminal	n	1,016		1,292			
		Abnormal	2	0.2	2	0.2	1.27 (0.18,9.05)	0.999
		Normal	1,014	99.8	1,290	99.8		
Smile	VII Facial	n	1,016		1,292			
		Abnormal	7	0.7	4	0.3	2.23 (0.67,7.41)	0.230
		Normal	1,009	99.3	1,288	99.7		
Palpebral Fissures	VII Facial	n	1,015		1,292			
		Abnormal	7	0.7	7	0.5	1.28 (0.45,3.65)	0.789
		Normal	1,008	99.3	1,285	99.5		
Balance	VIII Acoustic	n	1,015		1,292			
		Abnormal	2	0.2	1	0.1	2.55 (0.23,28.15)	0.586
		Normal	1,013	99.8	1,291	99.9		

TABLE 11-5. (continued)

Unadjusted Analyses for Cranial Nerve Function by Group

Variable	Cranial Nerve	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Gag Reflex	IX Glosso-pharyngeal	n	1,014		1,291			
		Abnormal	1	0.1	1	0.1	1.27 (0.08,20.38)	0.999
		Normal	1,013	99.9	1,290	99.9		
Speech	X Vagus	n	1,016		1,291			
		Abnormal	3	0.3	0	0.0	8.92 (0.46,172.89)[a]	0.085
		Normal	1,013	99.7	1,291	100.0		
Tongue Position Relative to Midline	X Vagus	n	1,015		1,292			
		Abnormal	3	0.3	0	0.0	8.94 (0.46,173.19)[a]	0.085
		Normal	1,012	99.7	1,292	100.0		
Palate and Uvula Movement	XI Spinal Accessory	n	1,014		1,291			
		Abnormal	2	0.2	1	0.1	2.55 (0.23,28.16)	0.586
		Normal	1,012	99.8	1,290	99.9		
Neck Range of Motion	XII Hypoglossal	n	1,016		1,292			
		Abnormal	61	6.0	84	6.5	0.92 (0.65,1.29)	0.666
		Normal	955	94.0	1,208	93.5		
Cranial Nerve Function Index		n	1,003		1,275			
		Abnormal	96	9.6	115	9.0	1.07 (0.80,1.42)	0.663
		Normal	907	90.4	1,160	91.0		
Cranial Nerve Function Index (Neck Range of Motion Excluded)		n	1,003		1,275			
		Abnormal	42	4.2	35	2.7	1.55 (0.98,2.44)	0.062
		Normal	961	95.8	1,240	97.3		

[a]Estimated relative risk and 95% confidence interval calculated after adding 0.5 to each cell.

TABLE 11-6.

Adjusted Analyses for Selected Variables of Cranial Nerve Function by Group

Variable	Statistic	Ranch Hand Number	Ranch Hand Percent	Comparison Number	Comparison Percent	Est. Relative Risk(95% C.I.)	p-Value	Covariate Remarks*
Neck Range of Motion	n	1,016		1,292		0.90 (0.63,1.27)	0.531	AGE(p<0.001) GRP*AGE (marginal:p=0.0501)
	Abnormal	61	6.0	84	6.5			
	Normal	955	94.0	1,208	93.5			
Cranial Nerve Function Index	n	1,003		1,275		1.07 (0.80,1.42)	0.666	AGE(p<0.001)
	Abnormal	96	9.6	115	9.0			
	Normal	907	90.4	1,160	91.0			
Cranial Nerve Function Index (Neck Range of Motion Excluded)	n	964		1,232		1.42 (0.88,2.30)	0.153	DIAB*INS(p=0.022) OCC*DRKYR(p=0.011) OCC*DIAB(p=0.015)
	Abnormal	38	3.9	34	2.8			
	Normal	926	96.1	1,198	97.2			
	Alternative Model—Includes Missing Drink-Year Participants[a,b]							
	n	1,003		1,271		1.56 (0.98,2.49)	0.061	DIAB*INS(p=0.017) OCC*DIAB(p=0.016)
	Abnormal	42	4.2	34	2.7			
	Normal	961	95.8	1,237	97.3			

*Abbreviations:

GRP: group
DIAB: diabetic class
INS: insecticide exposure
OCC: occupation
DRKYR: drink-years

[a]Lifetime alcohol consumption (total drink-years) not used as a covariate.

[b]79 missing drink-year participants: 4/39 Ranch Hands abnormal; 0/40 Comparisons abnormal.

TABLE 11-7.

Summary Table of Group-by-Covariate Interactions for Neurological Variables

Variable	Interaction	Stratification	Statistic	Group: Ranch Hands Number	Ranch Hands Percent	Group: Comparisons Number	Comparisons Percent	Adj. Relative Risk (95% C.I.)	p-Value
Neck Range of Motion	Group-by-Age	Born ≥ 1942	n	412		549			
			Abnormal	10	2.4	5	0.9	3.03 (1.02,9.00)	0.045
			Normal	402	97.6	544	99.1		
		Born 1923-1941	n	568		693			
			Abnormal	47	8.3	70	10.1	0.82 (0.55,1.21)	0.319
			Normal	521	91.7	623	89.9		
		Born ≤ 1922	n	36		50			
			Abnormal	4	11.1	9	18.0	(0.55 (0.16,1.97)	0.361
			Normal	32	88.9	41	82.0		
Pin Prick	Group-by-Diabetic Class	Abnormal	n	76		94			
			Abnormal	13	17.1	10	10.6	1.74 (0.71,4.24)	0.223
			Normal	63	82.9	84	89.4		
		Impaired	n	105		174			
			Abnormal	1	1.0	16	9.2	0.09 (0.01,0.69)	0.021
			Normal	104	99.0	158	90.8		
		Normal	n	822		1,005			
			Abnormal	45	5.5	53	5.3	1.02 (0.68,1.54)	0.920
			Normal	777	94.5	952	94.7		
Tremor	Group-by-Insecticides Exposure	Exposed to Insecticides	n	703		683			
			Abnormal	22	3.1	8	1.2	2.60 (1.15,5.90)	0.022
			Normal	681	96.9	675	98.8		
		Not Exposed to Insecticide	n	313		605			
			Abnormal	4	1.3	11	1.8	0.69 (0.22,2.19)	0.532
			Normal	309	98.7	594	98.2		

The stratified analysis for neck range of motion showed a higher proportion of younger Ranch Hands with neck range of motion abnormalities than younger Comparisons (p=0.045). Although not statistically significant, middle-aged and older Comparisons had higher proportions of abnormalities than did the Ranch Hands.

Peripheral Nerve Status

Peripheral nerve integrity was assessed by light pin prick, light touch (cotton sticks), visual inspection (and palpation, if indicated) of muscle mass, vibratory sensation as measured at the ankle with a tuning fork of 128 Hz, three deep tendon reflexes (patellar, Achilles, and biceps), and the Babinski reflex. The unadjusted analyses are given in Table 11-8. As noted previously, the analyses of pin prick, light touch, and vibratory sensation excluded the 29 participants with peripheral edema. These results showed that peripheral nerve function did not vary significantly by group.

Adjusted analyses were performed by logistic regression on four peripheral nerve variables. The other variables had relatively sparse numbers of abnormalities. The covariates were age, race, occupation, drink-years of alcohol, diabetic class, and exposure to insecticides. These statistics are displayed in Table 11-9.

For the variables light touch, muscle status, and the Achilles reflex, group differences were nonsignificant; the results were nearly identical to the unadjusted analyses. For the variable pin prick, however, a significant group-by-diabetic class interaction (p=0.003) was observed. This interaction was explored and the results are depicted in Table 11-7. As shown, the interaction suggests a difference, due to a lower proportion of abnormal pin-prick results in Ranch Hand impaired diabetics than in Comparisons (Adj. RR: 0.09,95% C.I.: [0.01,0.69], p=0.021), whereas both the abnormal and normal diabetic classes showed no significant group differences.

Central Nervous System Coordination

CNS coordination was evaluated clinically with four variables: hand tremor, rapid finger-to-nose coordination, one-foot standing balance (modified Romberg sign), and observation of gait for at least 10 steps. In addition, a constructed variable, the CNS summary index, was derived by summarizing abnormalities from all four CNS variables. The unadjusted analyses of these five variables are shown in Table 11-10.

These results revealed no statistically significant group differences for the four primary CNS variables, although the borderline significance of tremor, with a higher proportion of abnormalities in the Ranch Hands, is interesting. The statistical power to detect a given relative risk was poor because of the small percentages of abnormalities. The CNS summary index was statistically significant, with Ranch Hands manifesting a higher proportion of abnormalities; this result should be interpreted with caution, however, since this index was constructed after the data were examined. Three of the five variables with sufficient proportions of abnormalities were adjusted by six covariates, and these results are summarized in Table 11-11.

TABLE 11-8.

Unadjusted Analyses for Peripheral Nerve Function by Group

Variable	Statistic	Group: Ranch Hand Number	Ranch Hand Percent	Group: Comparison Number	Comparison Percent	Est. Relative Risk (95% C.I.)	p-Value
Pin Prick	n	1,003		1,276			
	Abnormal	59	5.9	80	6.3	0.93 (0.66,1.32)	0.725
	Normal	944	94.1	1,196	93.7		
Light Touch	n	1,003		1,276			
	Abnormal	38	3.8	47	3.7	1.03 (0.67,1.59)	0.912
	Normal	965	96.2	1,229	96.3		
Muscle Status	n	1,016		1,292			
	Abnormal	26	2.6	33	2.6	1.00 (0.60,1.69)	0.999
	Normal	990	97.4	1,259	97.4		
Vibratory Sensation	n	1,003		1,276			
	Abnormal	11	1.1	10	0.8	1.40 (0.59,3.32)	0.510
	Normal	992	98.9	1,266	99.2		
Patellar Reflex	n	1,016		1,290			
	Abnormal	11	1.1	16	1.2	0.87 (0.40,1.89)	0.846
	Normal	1,005	98.9	1,274	98.8		
Achilles Reflex	n	1,009		1,284			
	Abnormal	58	5.7	75	5.8	0.98 (0.69,1.40)	0.999
	Normal	951	94.3	1,209	94.2		
Biceps Reflex	n	1,016		1,292			
	Abnormal	9	0.9	10	0.8	1.15 (0.46,2.83)	0.819
	Normal	1,007	99.1	1,282	99.2		
Babinski Reflex	n	1,011		1,287			
	Abnormal	4	0.4	5	0.4	1.02 (0.27,3.80)	0.999
	Normal	1,007	99.6	1,282	99.6		