sense in the lower extremities or of inner ear disease. Finally, the mental status examination is important in the CNS assessment. Extensive psychometric studies were conducted, as in previous examination cycles, and are reported in Chapter 9.

Of the eight historical variables analyzed, only the ICD-9-CM category of "other neurologic disorders" was found to have a significant positive association with the body burden of dioxin. In the maximal cohort, a statistically significant increase in the diseases included in this category was noted in association with the extrapolated initial level of serum dioxin. Also, for Ranch Hands with less than 18.6 years since service in Vietnam, there was a significant association with current levels of serum dioxin. These positive findings were no longer present after adjustment for age and military occupation. There was no apparent increase in the historical incidence of peripheral neuropathy in association with serum dioxin levels or in Ranch Hand participants relative to Comparisons. The serum dioxin analyses did not find a significant association with an increased risk of hereditary and degenerative diseases. This finding contrasted with the results from the previous report (36), which found that the incidence of hereditary and degenerative diseases differed significantly between the Ranch Hand and Comparison groups (5.5% versus 3.5%).

Related to the extrapolated initial level of serum dioxin, there were no significant associations noted in any of the directly measured physical examination variables. Several indices (neck range of motion and cranial nerve index) were found to have statistically significant but inconsistent associations with the current level of serum dioxin without evidence for a dose-response effect. Participants more removed from their tour of duty in Vietnam were at slightly greater risk. Significant differences between current dioxin categories were not noted in either index.

Of the neurological disorders considered, only peripheral neuropathy has been clearly shown to be associated with TCDD exposure in other studies. Of the eight peripheral motor and sensory indices examined, no significant associations were found with the initial, current serum dioxin levels, or categorical dioxin levels.

In the adjusted analysis of the current serum dioxin, participants less removed from active duty in Vietnam were more likely to show abnormalities in coordination and in the CNS index in a pattern consistent with a dose-response effect. Further, for both indices, Ranch Hands with higher levels of serum dioxin were at increased risk relative to Comparisons, particularly with respect to coordination (Adj. RR=18.30; p=0.001). In the longitudinal analysis of the CNS index under the maximal assumption, there was a marginally significant positive association with initial dioxin. Ranch Hands with the highest levels of initial dioxin had a higher incidence of abnormalities (5.2%) than those in the medium (3.5%) or low (2.4%) initial dioxin categories. Though it would be difficult to explain these results on the basis of cause and effect, they are consistent with those described in the 1987 report and will be evaluated in future examination cycles.

In summary, data analyzed in this chapter revealed no consistent evidence for clinically significant neurological disease associated with the current body burden of dioxin. Statistically significant associations were noted but not in patterns consistent with a dose-response effect.

SUMMARY

The neurological assessment focused on extensive physical examination data for cranial nerve function, peripheral nerve status, and CNS coordination processes. Verified histories of neurological diseases were also examined. Three sets of analyses were performed to assess the association between dioxin and the neurological variables. Table 8-38 summarizes the results of the initial dioxin analyses. Table 8-39 presents the results of the current dioxin and time since tour analyses, and Table 8-40 summarizes the categorized current dioxin analyses. Table 8-41 lists the dioxin-by-covariate interactions found in the adjusted analyses.

Questionnaire Variables

Information from the questionnaire was verified and grouped into eight categories of neurological diseases: inflammatory diseases, hereditary and degenerative diseases, peripheral disorders, disorders of the eye, external otitis, tympanic membrane disorders, hearing loss, and other neurological diseases.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not significantly associated with inflammatory diseases, hereditary and degenerative diseases, peripheral disorders, eye disorders, tympanic membrane disorder, and otitis. There was a marginally significant increased risk of hearing loss under the minimal assumption after adjustment for age, but the relative risk was not significant under the maximal assumption.

Under both assumptions, initial dioxin was associated with a significant increased risk of conditions in the other neurological disorders category after adjusting for age. However, further investigation indicated that this was related to a significant association between occupation and other neurological disorders. Independent of group membership, officers had a much lower incidence of other neurological disorders than either enlisted flyers or enlisted groundcrew. Ranch Hand officers also had the lowest levels of dioxin in general. After adjusting for age and occupation, the association between initial dioxin and other neurological disorders became nonsignificant under both assumptions.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin and time since tour analyses were generally not significant for the questionnaire variables. Under the maximal assumption, the association between current dioxin and otitis differed significantly between time strata, but this was due to a significant decreased risk of otitis for Ranch Hands with a later tour. Adjusting for age, current dioxin was significantly associated with other neurological disorders in both time strata under the maximal assumption, but these associations became nonsignificant when occupation was included in the model.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The categorized current dioxin analyses of the questionnaire variables displayed few significant results. The unadjusted analyses found a marginally significant difference in the prevalence of hearing loss among the four current dioxin categories, with a significant decreased risk in the high category relative to the background category. Ranch Hands in the

TABLE 8-38.

Summary of Initial Dioxin Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted		Adjusted	
Variable	Minimal	Maximal	Minimal	Maximal
Questionnaire				
Inflammatory Diseases	NS	NS	--	--
Hereditary and Degenerative Diseases	ns	ns	ns	ns
Peripheral Disorders	NS	NS	NS	NS
Disorders of the Eye	NS	NS	NS	NS
Tympanic Membrane Disorder	ns	NS	ns	NS
Otitis	NS	ns	NS	ns
Hearing Loss	ns	ns	NS*	NS
Other Neurological Disorders	NS	+<0.001	+0.037[a]	+<0.001[a]
Other Neurological Disorders	--	--	ns[b]	NS[b]
Physical Examination				
Cranial Nerve Function				
Smell	ns	ns	ns	ns
Visual Fields	--	--	--	--
Light Reaction	NS	ns	NS	ns
Ocular Movement	ns	NS	NS	NS
Facial Sensation	ns	NS	ns	NS
Smile	NS	NS	NS	NS
Palpebral Fissure	NS	NS	NS	NS
Balance[c]	NS	NS	--	--
Speech	--	--	--	--
Neck Range of Motion	NS	ns	*** (NS*)	*** (NS)
Cranial Nerve Index	NS	ns	NS*	** (NS)
Cranial Nerve Index Without Range of Motion	NS	NS	NS	NS
Peripheral Nerve Status				
Pin Prick	NS	NS	** (NS)	** (NS)
Light Touch	ns	NS	NS	ns
Muscle Status	NS	NS	NS	NS
Vibration	ns	NS	ns	NS
Patellar Reflex	NS	NS	NS	NS
Achilles Reflex	ns	NS	ns	NS

TABLE 8-38. (Continued)

Summary of Initial Dioxin Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

Variable	Unadjusted		Adjusted	
	Minimal	Maximal	Minimal	Maximal
Peripheral Nerve Status (continued)				
Achilles Reflex[d]	--	--	NS	NS*
Biceps Reflex	--	--	--	--
Babinski Reflex	NS	NS	--	--
Central Nervous System Coordination Processes				
Tremor	NS	NS	NS	NS
Coordination	NS	NS	NS	NS
Coordination[d]	--	--	NS	NS*
Romberg Sign[c]	NS	NS	--	--
Gait	NS	NS	NS	NS
CNS Index	NS	NS*	** (NS)	** (+0.050)

[a]Adjusted for age.

[b]Adjusted for age and occupation. Appendix Table G-3 presents a detailed description of these analyses.

[c]Balance same as Romberg sign.

[d]Adjusted results presented for model without diabetic class. Appendix Table G-2 presents a detailed description of this analysis.

+: Relative risk 1.00 or greater.

--: Analysis not applicable or not performed due to the sparse number of abnormalities.

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

NS*/ns*: Marginally significant ($0.05<p\leq0.10$).

** (NS)/** (ns): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

** (0.050): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); significant ($p=0.050$) when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

*** (NS): Log_2 (initial-dioxin)-by-covariate interaction ($p\leq0.01$); not significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

*** (NS*): Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); marginally significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

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

A capital "NS" denotes relative risk 1.00 or greater; a lowercase "ns" denotes relative risk less than 1.00.

TABLE 8-39.

Summary of Current Dioxin and Time Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Inflammatory Diseases	--	--	--	--	--	--
Hereditary and Degenerative Diseases	NS	ns	NS	NS	ns	NS
Peripheral Disorders	NS	ns	NS	NS	ns	NS
Disorders of the Eye	NS	NS	NS	NS	NS	NS
Tympanic Membrane Disorder	ns	NS	ns	ns	ns	ns
Otitis	NS	ns	ns	+0.032	-0.012	ns
Hearing Loss	NS	ns	ns	ns	ns	ns*
Other Neurological Disorders	ns	NS	NS	ns	+0.002	NS
Physical Examination						
Cranial Nerve Function						
Smell	--	ns	--	--	ns	--
Visual Fields	--	--	--	--	--	--
Light Reaction	--	ns	--	NS	ns	NS
Ocular Movement	--	--	ns	--	--	ns
Facial Sensation	--	NS	--	--	NS	--
Smile	--	--	NS*	--	--	NS
Palpebral Fissure	NS	ns	NS	NS	ns	NS
Balance[a]	--	--	ns	--	--	NS
Speech	--	--	--	--	--	--
Neck Range of Motion	NS	ns	NS	+0.024	-0.024	NS
Cranial Nerve Index	NS	ns	NS	+0.021	-0.027	NS
Cranial Nerve Index Without Range of Motion	NS	ns	NS	NS	ns	NS
Peripheral Nerve Status						
Pin Prick	NS	ns	NS	NS	NS	NS
Light Touch	+0.023	ns	NS	NS	ns	NS
Muscle Status	ns	NS	ns	ns	NS	NS
Vibration	ns	ns	ns	ns	NS	ns
Patellar Reflex	ns	NS	NS	ns	NS	NS

TABLE 8-39. (Continued)

Summary of Current Dioxin and Time Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Peripheral Nerve Status (continued)						
Achilles Reflex	+0.049	ns*	NS	NS	ns	NS
Biceps Reflex	--	--	--	--	--	--
Babinski Reflex	--	--	ns	--	--	NS
Central Nervous System Coordination Processes						
Tremor	ns	NS	ns	ns	NS	ns
Coordination	ns	NS	ns	ns	NS*	ns
Romberg Sign[a]	--	--	ns	--	--	NS
Gait	ns	NS	NS	NS	NS	NS
CNS Index	ns	NS	NS	ns	NS*	NS

[a]Balance same as Romberg sign.

+: C*T: Relative risk for ≤18.6 category less than relative risk for <18.6 category.
≤18.6: Relative risk 1.00 or greater.

-: ≤18.6: Relative risk less than 1.00.

--: Analysis not performed due to the sparse number of abnormalities.

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

NS*/ns*: Marginally significant ($0.05<p\leq0.10$).

Note: P-value given if $p\leq0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.
A capital "NS" denotes relative risk for ≤18.6 category less than relative risk for >18.6 category or relative risk 1.00 or greater; a lowercase "ns" denotes relative risk for <18.6 category greater than relative risk for >18.6 category or relative risk less than 1.00.

TABLE 8-39. (Continued)

Summary of Current Dioxin and Time Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Inflammatory Diseases	--	--	--	--	--	--
Hereditary and Degenerative Diseases	NS	ns	NS	NS	NS	NS
Peripheral Disorders	NS	ns	NS	NS	ns	NS
Disorders of the Eye	NS	NS	NS	NS	NS	NS
Tympanic Membrane Disorder	ns	NS	ns	ns	NS	ns
Otitis	NS	ns	NS	+0.031	-0.020	NS
Hearing Loss	NS	NS	NS	ns	NS	NS
Other Neurological Disorders[b]	ns	+0.041	NS	ns*	+<0.001	+0.014
Other Neurological Disorders[c]	ns	NS	ns	ns	NS	ns
Physical Examination						
Cranial Nerve Function						
Smell	--	--	--	--	--	--
Visual Fields	--	--	--	--	--	--
Light Reaction	--	--	--	--	--	--
Ocular Movement	--	--	--	--	--	--
Facial Sensation	--	--	--	--	--	--
Smile	--	--	--	--	--	--
Palpebral Fissure	NS	ns	NS	NS	ns	NS
Balance[a]	--	--	--	--	--	--
Speech	--	--	--	--	--	--
Neck Range of Motion	NS	NS	+0.017	+0.026	ns	+0.029
Cranial Nerve Index	NS	NS	+0.033	+0.023	ns	+0.034
Cranial Nerve Index Without Range of Motion	NS	ns	NS	NS	ns	NS
Peripheral Nerve Status						
Pin Prick	** (NS)	** (ns)	** (NS)	** (NS)	** (NS)	** (NS)
Light Touch	+0.048	ns	NS	NS	ns	NS
Muscle Status	ns	NS	NS	ns	NS	NS
Vibration	ns	ns	ns	ns	NS	NS

TABLE 8-39. (Continued)

Summary of Current Dioxin and Time Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Peripheral Nerve Status (continued)						
Patellar Reflex	ns	NS	ns	ns	NS	NS
Achilles Reflex	NS*	ns	NS	NS	ns	NS*
Biceps Reflex	--	--	--	--	--	--
Babinski Reflex	--	--	--	--	--	--
Central Nervous System Coordination Processes						
Tremor	ns	NS	ns	** (ns)	** (NS)	** (ns)
Coordination	ns	NS*	NS	ns*	+0.019	NS
Romberg Sign[a]	--	--	--	--	--	--
Gait	ns	NS	NS	ns	NS	NS
CNS Index	ns	NS	NS	ns	+0.029	NS

[a]Balance same as Romberg sign.

[b]Adjusted for age.

[c]Adjusted for age and occupation. Appendix Table G-3 presents a detailed description of these analyses.

+: C*T: Relative risk for ≤18.6 category less than relative risk for >18.6 category.
≤18.6 or >18.6: Relative risk 1.00 or greater.

-: ≤18.6: Relative risk less than 1.00.

--: Analysis not performed due to the sparse number of abnormalities.

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

NS*/ns*: Marginally significant ($0.05<p\leq0.10$).

** (NS)/** (ns): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

Note: P-value given if $p\leq0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.
>18.6: Log_2 (current) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.
A capital "NS" denotes relative risk for ≤18.6 category less than relative risk for >18.6 category or relative risk 1.00 or greater; a lowercase "ns" denotes relative risk for ≤18.6 category greater than relative risk for >18.6 category or relative risk less than 1.00.

TABLE 8-40.

Summary of Categorized Current Dioxin Analyses for Neurological Variables (Ranch Hands and Comparisons)

Variable	Unadjusted			
	All	Unknown versus Background	Low versus Background	High versus Background
Questionnaire				
Inflammatory Diseases	NS	NS	ns	NS
Hereditary and Degenerative Diseases	NS	NS	ns	ns
Peripheral Disorders	NS	ns	ns	NS
Disorders of the Eye	NS	NS	NS	NS
Tympanic Membrane Disorder	NS	ns	NS	NS
Otitis	NS	NS	NS	ns
Hearing Loss	NS*	ns	ns	-0.009
Other Neurological Disorders	0.014	ns*	NS*	NS
Physical Examination				
Cranial Nerve Function				
Smell	NS	ns	NS	ns
Visual Fields	NS	ns	ns	ns
Light Reaction	NS	ns	ns	NS
Ocular Movement	NS	ns	NS	ns
Facial Sensation	NS	ns	ns	ns
Smile	NS	ns	ns	ns
Palpebral Fissure	NS	ns	NS	NS
Balance[a]	NS	--	NS	NS
Speech	NS	ns	NS	ns
Neck Range of Motion	NS	NS	NS	ns
Cranial Nerve Index	NS	ns	NS	ns
Cranial Nerve Index Without Range of Motion	NS	ns	NS	ns
Peripheral Nerve Status				
Pin Prick	NS	ns	ns	NS
Light Touch	NS	ns	ns	ns
Muscle Status	NS	ns	ns	ns
Vibration	NS	ns	NS	NS
Patellar Reflex	NS	NS	NS	NS

TABLE 8-40. (Continued)

Summary of Categorized Current Dioxin Analyses for Neurological Variables (Ranch Hands and Comparisons)

Variable	Unadjusted			
	All	Unknown versus Background	Low versus Background	High versus Background
Peripheral Nerve Status (continued)				
Achilles Reflex	NS	ns	NS	ns
Biceps Reflex	NS	ns	ns	ns
Babinski Reflex	NS	NS	ns	NS
Central Nervous System Coordination Processes				
Tremor	NS	ns	ns	NS
Coordination	NS*	NS	NS	+0.007
Romberg Sign[a]	NS	--	NS	NS
Gait	NS	NS	NS	NS
CNS Index	NS	NS	ns	+0.050

[a]Balance same as Romberg sign.
+: Relative risk 1.00 or greater.
-: Relative risk less than 1.00.
--: Analysis not performed due to the absence of abnormalities.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater; a lowercase "ns" denotes relative risk less than 1.00; a capital "NS" in the first column does not imply directionality.

TABLE 8-40. (Continued)

Summary of Categorized Current Dioxin Analyses for Neurological Variables (Ranch Hands and Comparisons)

Variable	All	Adjusted: Unknown versus Background	Adjusted: Low versus Background	Adjusted: High versus Background
Questionnaire				
Inflammatory Diseases	--	--	--	--
Hereditary and Degenerative Diseases	NS	NS	ns	ns
Peripheral Disorders	NS	ns	ns	NS
Disorders of the Eye	NS	NS	NS	NS
Tympanic Membrane Disorder	NS	ns	NS	NS
Otitis	NS	NS	NS	ns
Hearing Loss	NS	ns	ns	ns
Other Neurological Disorders[b]	<0.001	-0.041	NS*	+0.005
Other Neurological Disorders[c]	NS	NS	NS	NS
Physical Examination				
Cranial Nerve Function				
Smell	NS	ns	NS	--
Visual Fields	--	--	--	--
Light Reaction	NS	ns	--	NS
Ocular Movement	NS	ns	NS	--
Facial Sensation	NS	--	ns	ns
Smile	NS	ns	ns	NS
Palpebral Fissure	NS	ns	NS	NS
Balance[a]	--	--	--	--
Speech	--	--	--	--
Neck Range of Motion	** (NS)	** (ns)	** (NS)	** (NS)
Cranial Nerve Index	NS	ns	NS	ns
Cranial Nerve Index Without Range of Motion	** (NS)	** (ns*)	** (NS)	** (ns)
Peripheral Nerve Status				
Pin Prick	NS	ns	ns	NS
Light Touch	NS	NS	ns	ns
Muscle Status	** (NS)	** (ns)	** (ns)	** (NS)
Vibration	NS	ns	NS	NS

TABLE 8-40. (Continued)

Summary of Categorized Current Dioxin Analyses for Neurological Variables (Ranch Hands and Comparisons)

Variable	All	Adjusted: Unknown versus Background	Adjusted: Low versus Background	Adjusted: High versus Background
Peripheral Nerve Status (continued)				
Patellar Reflex	NS	NS	NS	NS*
Achilles Reflex	** (NS)	** (ns)	** (NS)	** (NS)
Biceps Reflex	--	--	--	--
Babinski Reflex	--	--	--	--
Central Nervous System Coordination Processes				
Tremor	NS	ns	ns	NS
Coordination	** (0.006)	** (NS*)	** (NS)	** (+0.001)
Romberg Sign[a]	--	--	--	--
Gait	** (NS)	** (NS)	** (NS)	** (NS)
CNS Index	** (NS)	** (NS)	** (ns)	** (+0.023)

[a]Balance same as Romberg sign.
[b]Adjusted for age.
[c]Adjusted for age and occupation. Appendix Table G-3 presents a detailed description of this analysis.
+: Relative risk 1.00 or greater.
-: Relative risk less than 1.00.
--: Analysis not performed due to the absence of abnormalities.
NS/ns: Not significant ($p>0.10$).
NS*: Marginally significant ($0.05<p\leq0.10$).
** (NS)/** (ns): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.
** (NS*)/** (ns*): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); marginally significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.
**(...): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table G-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater; a lowercase "ns" denotes relative risk less than 1.00; a capital "NS" in the first column does not imply directionality.

TABLE 8-41.

Summary of Dioxin-by-Covariate Interactions from Adjusted Analysis of Neurology Variables

Variable	Assumption	Covariate
Model 1: Log_2 (Initial Dioxin)		
Neck Range of Motion	Minimal	RACE, DIAB
Neck Range of Motion	Maximal	DIAB
Cranial Nerve Index	Maximal	DIAB
Pin Prick	Minimal	DIAB
Pin Prick	Maximal	DIAB
CNS Index	Minimal	AGE
CNS Index	Maximal	AGE
Model 2: Log_2 (Current Dioxin) and Time		
Pin Prick	Minimal	DRKYR
Pin Prick	Maximal	DRKYR
Tremor	Maximal	AGE
Model 3: Ranch Hands and Comparisons by Current Dioxin Category		
Neck Range of Motion	--	DIAB
Cranial Nerve Index Without Range of Motion	--	INS
Muscle Status	--	DIAB
Achilles Reflex	--	RACE
Coordination	--	AGE
Gait	--	DIAB
CNS Index	--	AGE

high current dioxin category had the lowest incidence of hearing loss. However, after adjustment for age, these contrasts became nonsignificant because Ranch Hands in the high current dioxin category were younger on average than men in the other categories. The incidence of conditions in the category of other neurological disorders differed significantly among categories whether unadjusted or adjusted for age, but when occupation was included in the model all contrasts were not significant.

Physical Examination Variables

The neurological assessment analyzed 12 variables to examine the association between dioxin and cranial nerve function (smell, visual fields, light reaction, ocular movement, facial sensation, smile, palpebral fissure, balance, speech, neck range of motion, a cranial nerve index, and the index without range of motion). Pin prick, light touch, muscle status, vibration, patellar reflex, Achilles reflex, biceps reflex, and the Babinski reflex were analyzed to assess peripheral nerve status. The CNS coordination processes were based on tremor, coordination, Romberg sign (balance), gait and a CNS summary index. There were few abnormalities for many of these variables, limiting the statistical power to detect a significant difference.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the unadjusted initial dioxin analyses were not significant for all neurological examination variables, although the relative risk was marginally more than 1 for the CNS index under the maximal assumption. The adjusted minimal analyses found that there was a marginally significant increased risk for range of motion. Under the maximal assumption, the adjusted analyses of the Achilles reflex and coordination displayed a relative risk that was marginally more than 1 when diabetic class was excluded from the model. The risks were not significant when diabetic class was in the model. After adjusting for age and lifetime alcohol history, the adjusted relative risk of an abnormal CNS index was significantly more than 1 under the maximal assumption.

Under one or both assumptions, the adjusted analyses detected significant initial dioxin-by-diabetic class interactions for range of motion, the cranial nerve index, and pin prick. Stratified results revealed significant or marginally significant positive associations between initial dioxin and these variables for diabetic Ranch Hands. By contrast, the relative risks were less than 1, although not significant (marginally significant for pin prick under the maximal assumption), for diabetically impaired individuals.

Under both the minimal and maximal assumptions, the adjusted analyses for the CNS index found a significant interaction between initial dioxin and age. Categorizing age to explore the interaction revealed a significant positive association between initial dioxin and the CNS index for Ranch Hands born before 1942. The relative risk was not significant for younger Ranch Hands.

Under the maximal assumption, the longitudinal analyses found that initial dioxin was associated with a marginally significant decreased risk of developing a cranial nerve index abnormality between 1985 and 1987, and a marginally significant increased risk of developing a CNS index abnormality. The initial dioxin longitudinal analyses under the minimal assumption were not significant.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin and time since tour analyses were generally not significant for the neurological examination variables. Under the minimal assumption, the adjusted current dioxin and time analyses displayed a significant current dioxin-by-time interaction for light touch and a marginally significant interaction for the Achilles reflex, but the within time stratum results were not significant. For Ranch Hands in the minimal cohort with an early tour, there was a marginally significant positive association between current dioxin and smile in the unadjusted analysis and a significant increased risk of range of motion abnormalities and an abnormal cranial nerve index in the adjusted analyses.

The adjusted maximal analyses found a significant current dioxin-by-time interaction for range of motion and for the cranial nerve index. Consistent with the adjusted minimal analysis, the relative risk for both these variables was significantly more than 1 for Ranch Hands with an early tour. The adjusted maximal analyses also detected a significant increased risk for coordination and the CNS index for Ranch Hands with a later tour. The adjusted relative risk of an abnormal Achilles reflex was marginally more than 1 for Ranch Hands in the maximal cohort with an early tour.

Other adjusted analyses were not significant except for a significant current dioxin-by-time-by-lifetime alcohol history interaction for pin prick and a significant current dioxin-by-time-by-age interaction for tremor.

Under the maximal assumption, the longitudinal analyses of the cranial nerve index found a marginally significant current dioxin-by-time interaction that was due to a significant decreased risk of developing an abnormality between 1985 and 1987 for Ranch Hands with a later tour. The current dioxin and time longitudinal analyses of the cranial nerve index were not significant under the minimal assumption. Under both assumptions, the interaction between current dioxin and time was not significant in the longitudinal analyses of the CNS index, but the relative risk of developing an abnormality was marginally more than 1 for Ranch Hands in the maximal cohort with a later tour.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analyses found a marginally significant difference in the prevalence of coordination abnormalities among current dioxin categories, but otherwise the overall contrast was not significant for the other examination variables. In the unadjusted analyses, the high versus background contrast exhibited a significant increased risk for both coordination and the CNS index. The results for coordination are consistent with previous results from the 1987 study, which found a significant group difference. No other contrasts were significant in the unadjusted analyses.

The adjusted analyses displayed comparable findings. The overall contrast was significant in the adjusted analysis of coordination, but not for the other variables. In the adjusted analyses of coordination and the CNS index, the relative risk for the high versus background contrast was significantly more than 1. Several contrasts became marginally significant after covariate adjustment. Relative to the background category, there was a marginally significant increased risk of patellar reflex abnormalities in the high current dioxin category, a marginally significant increased risk of coordination abnormalities in the unknown

category, and a marginally significant decreased risk of cranial nerve index abnormalities without range of motion in the unknown category.

The adjusted analyses encountered several categorized current dioxin-by-covariate interactions, which are listed in Table 8-41. The interaction between categorized current dioxin and age was significant for the CNS index. For older Ranch Hands, the relative risk was significantly more than 1 for the high versus background contrast. This is consistent with the results for the CNS index from the initial dioxin analyses. Stratified results to explore the other interactions disclosed no consistent pattern indicative of a dioxin effect. The longitudinal analysis of the cranial nerve index displayed a marginally significant decreased risk of developing an abnormality for the high current dioxin category relative to the background category. The longitudinal analysis of the CNS index showed no significant results, but the high current dioxin category had the highest incidence.

CONCLUSION

Overall, the neurological assessment did not indicate that dioxin was associated with neurological disease, although some analyses revealed a significant association with the 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 previous report found that Ranch Hands had a significantly higher incidence of hereditary and degenerative diseases (mostly benign essential tremor) than Comparisons, but the serum dioxin analyses provided no support that dioxin levels were associated significantly with an increased risk. The adjusted categorized current dioxin analyses for coordination found that the relative risk was significantly greater than 1 for Ranch Hands in the high current dioxin category. This is consistent with the previous report's finding that the Ranch Hand group had significantly more coordination abnormalities than the Comparison group (1.5% versus 0.6%). The serum dioxin analyses showed significant associations with the CNS index, including a marginally significant association with initial dioxin under the maximal assumption in the longitudinal analyses.

CHAPTER 8

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CHAPTER 9

PSYCHOLOGICAL ASSESSMENT

INTRODUCTION

Background

Chronic psychological disorders rarely are recognized as primary clinical endpoints following exposure to chlorophenols, phenoxy herbicides, and dioxin. Experimental animal studies provide little insight into potential psychological consequences of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure in humans. Signs of toxicity in animals (lethargy, stupor, poor coordination, lack of feeding, and agitation) have been observed in multiple studies involving many species and have been attributed to the "wasting syndrome" of multiorgan toxicity rather than to primary central nervous system (CNS) toxicity (1).

A recent study of monkeys perinatally exposed to TCDD (2) is much more relevant to human research. Though the results were not uniform, subtle and selective deficits were noted in learning with TCDD-exposed monkeys that exhibited retarded learning of shape but not of spatial or color reversals.

Studies attempting to define human psychological/behavioral disorders related to TCDD exposure often are flawed by a number of limitations including the bias of self-reporting, the lack of confirmation by psychological testing, and the unreliable indices of exposure. Using chloracne as a reliable marker for high-level exposure, early studies of industrial chemical workers provided the first suggestion of psychological effects. Studies shortly after a Nitro, West Virginia, accident in 1949 documented nervousness, fatigue, irritability, cold intolerance, and decreased libido in many of the workers with chloracne. Most of these symptoms resolved over a 4-year period (3, 4). Two followup studies of expanded plant cohorts in 1979 noted a strong association between chloracne and reported symptoms of diminished libido, sexual dysfunction, and insomnia (5, 6). None of these studies included validation by neurobehavioral testing.

Other industrially based studies reported a wide range of acute and subacute subjective symptoms including fatigue, decreased libido, impotence, sleep disturbances, reduced emotional responses, sensory deficits, reading difficulties, memory loss, and emotional disorders (7-13). One study found a relationship between chloracne and hypomania as reflected in the Minnesota Multiphasic Personality Inventory (MMPI) (14). Another study noted that two of three chemists involved in the synthesis of TCDD developed marked personality changes (15). Although data interpretation problems exist, a Czechoslovakian 10-year followup study cited eight cases of severe dementia in exposed workers and reported that symptoms of anxiety and depression decreased over the followup period (13).

A contemporary cross-sectional morbidity study of a mobile-home park environmentally contaminated with dioxin documented psychological changes in exposed residents (16). Significant abnormalities were recorded in the exposed group for the tension/anxiety and anger/hostility scales of the Profile of Mood States Inventory as well as the vocabulary

subtest of the Wechsler Adult Intelligence Scale. However, cerebral function, as assessed by the Halstead-Reitan Battery (HRB), revealed no significant group differences.

Many epidemiologic studies have confirmed that the Vietnam War exacted an emotional toll of its veterans, particularly those who served in heavy combat. The possibility of occult disease consequent to herbicide exposure has introduced an additional element of uncertainty with its own set of adverse psychological implications. Relevant to this is a recent study of the psychological characteristics of 153 Vietnam veterans with comparable combat experience. Fifty-eight of these veterans reported moderate to high herbicide exposure in contrast to 95 veterans with minimal or no exposure. The perceived exposed cohort scored significantly higher on MMPI scales F, hypochondriasis, depression, paranoia, psychasthenia, schizophrenia, mania, and social introversion (17).

In addition to unreliable exposure estimates, this study of psychopathology in veterans was further complicated by the confounding effects of combat stress and the post-traumatic stress disorder (PTSD). In 1980, the American Psychiatric Association established the term *post-traumatic stress disorder* to define a condition caused by extreme psychic trauma; e.g., natural disaster, war, imprisonment, or torture (18). PTSD comprises symptoms of anxiety, "powder-keg" anger, depression, irritability, restlessness, recurrent intrusive dreams, flashbacks, and sleeplessness. Quiescent PTSD may be reactivated acutely in some individuals by a specific triggering event (19). Although a concise definition of PTSD exists, the best means of diagnosing it is controversial. Some investigators prefer a full and thorough clinical interview (20) while others favor empiric symptom scales (15). Each method serves a different, but highly related, purpose: clinical diagnosis in individuals versus an epidemiologic and statistical contrast of groups.

The prevalence of PTSD in Vietnam veterans is unknown; even the qualitative assessments of "common" or "rare" are debatable (20, 21). Eighteen percent of the nearly 100,000 Vietnam veterans registered in the Veterans Administration's Agent Orange Registry in 1983 complained of nervousness and 10 percent cited personality disorders (22). In a group of 132 veterans included in the Registry (most of whom were selected for inclusion in the study based on referral for psychotherapy), 53 percent met criteria for PTSD, based on symptoms of sleep disorders (53%), mood depression (36%), suicidal thoughts (35%), and irritability (31%) (23).

In another large study conducted by the Veterans Administration that focused on the association between Vietnam service and combat experience, eight PTSD indices (24) found a high incidence (16%) of PTSD in veterans of the Vietnam era. Though the study was recently published, the data were collected in 1979 before the public controversy surrounding the potential health consequences of exposure to Agent Orange. After adjustment for the potential confounding effects of military service and demographic factors, the level of combat exposure was significantly associated with all eight symptoms of PTSD in a dose-response pattern.

Many studies have attempted to investigate the relationship between PTSD and herbicide exposure in Vietnam veterans. The methods employed to determine exposure include self-reporting, use of chloracne symptoms (both self-reported and medically

diagnosed), and various attempts to link the geographic location of a veteran during service in Vietnam to areas of herbicide use. All of these methods have questionable validity. Self-reporting has been shown to be highly inaccurate for most applications (25). One study in which chloracne was used as an index of exposure examined 6 Vietnam veterans and 25 control subjects selected from the same sample group. Evidence was found for significant psychological disorders in the exposed subjects based on the results of a neuropsychological battery (26). Principal limitations of the study included the small sample size and lack of histologic confirmation of chloracne diagnosis.

The probabilistic approach is a more recent method used to determine herbicide exposure in Vietnam veterans. To develop probabilities for exposure, one study used data based on self-reported locations of service in Vietnam and Department of Defense records on locations where herbicides were employed (25). Based on the resulting probability distribution, 100 randomly selected Vietnam veterans were assessed for psychological problems and for self-reporting bias in symptoms. A similar incidence of psychological disorders was noted in the two groups using the probabilistic approach. In contrast, by self-reported exposure estimates, significant group differences were found. The authors concluded that self-reported indices of exposure were unreliable and that psychological symptomatology was significantly influenced by individual perception of exposure.

A larger study using the probabilistic approach selected 6,810 American Legionnaires who served during the Vietnam War (27). The group was divided into those who served in Southeast Asia (SEA) and those who served elsewhere at the same time. Those who served in SEA were considered the "possibly exposed" group (including 102 known handlers of herbicides); those who served elsewhere were considered unexposed. The probability of exposure was based on the time and location of service of each veteran and the time(s) of herbicide use in each area as identified from data released by the Army Joint Services Environmental Support Group. The level of combat experience was evaluated along with a number of social and behavioral effects. The results of the study showed that though herbicide exposure independently could not predict reported psycho-social outcomes, it could anticipate the outcomes when used as a cross-product with combat, indicating that a synergistic effect may be occurring (28). Reported outcomes were not verified by medical records review or psychological testing and exposure was not verified.

Though not specifically designed to investigate endpoints from Agent Orange exposure, the Vietnam Experience Study (VES) by the U.S. Centers for Disease Control included comprehensive psychological testing in Vietnam and non-Vietnam veterans (29). Results revealed an increased incidence of psychological dysfunction related to service in Vietnam including depression (4.5% of Vietnam veterans versus 3.2% in non-Vietnam veterans), anxiety (4.9% versus 3.2%), and alcohol abuse or dependence (13.7% versus 9.2%).

Lacking a valid index of herbicide exposure, research efforts to date can be summarized as contributing a great deal to our understanding of the psychological consequences associated with military service in Vietnam but very little to resolving the question of behavioral endpoints to TCDD toxicity. Further insight in this regard must await additional studies based on more accurate methods of determining the body burden of dioxin.

More detailed summaries of the pertinent scientific literature for the psychological assessment can be found in the report of the previous analyses of the 1987 examination data (30).

Summary of Previous Analyses of the 1987 Examination Data

The psychological assessment was based on verified psychological disorders; reported sleep disorders; and two clinical psychological tests, the Symptom Check List-90-Revised (SCL-90-R) and the Millon Clinical Multiaxial Inventory (MCMI). The verified data on lifetime psychological disorders showed no group differences for psychoses, drug dependence, and anxiety. However, marginally more Ranch Hands than Comparisons had a verified history of alcohol dependence and "other neuroses" based on unadjusted analyses. The Ranch Hands reported experiencing great or disabling fatigue during the day and talking in their sleep more frequently than the Comparisons. No group differences were detected in the other 13 sleep disorder variables in the unadjusted analyses. Although no significant differences between the Ranch Hands and Comparisons were found in the unadjusted analyses of the 12 SCL-90-R variables, the Ranch Hands had marginally more abnormalities than the Comparisons for depression, somatization, and an index of the general severity of symptoms. The results of the unadjusted analyses of the MCMI scores revealed that the Ranch Hands had significantly higher mean antisocial and paranoid scores than the Comparisons. Marginally significant differences were identified on the narcissistic and psychotic delusion scores, where the mean score of the Ranch Hands exceeded that of the Comparisons. After adjustment for the covariates, a significant difference remained on the narcissistic score. The Comparisons had a significantly higher mean dependent score than the Ranch Hands. Significant group-by-covariate interactions were frequently noted in the adjusted analyses, which made direct contrast of the two groups difficult.

Parameters of the Psychological Assessment

Dependent Variables

Questionnaire and physical examination data were used in the psychological assessment.

Questionnaire Data

At the face-to-face interview of the 1987 examination, each participant was asked whether he had a mental or emotional disorder since the date of his last interview. Reported disorders for which treatment was obtained were subsequently verified by reviews of medical records. Information on verified psychological disorders from the 1987 examination was combined with verified disorders from the Baseline and 1985 examinations, and a series of dependent variables regarding verified history of psychological disorders was created. In particular, the verified histories of psychoses, alcohol dependence, drug dependence, anxiety, and an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic code-based category of "other neuroses" (ICD codes 300-302, 305-309, and 311) were studied. Participants with a verified pre-SEA history of a psychological disorder were excluded from the analyses pertaining to that disorder.

Each participant was also asked a series of questions regarding sleep problems (31). Each participant was asked whether he had a current or past problem with the following 12

sleep disorders: (1) trouble falling asleep, (2) waking up during the night, (3) waking up too early and can't go back to sleep, (4) waking up unrefreshed, (5) involuntarily falling asleep during the day, (6) great or disabling fatigue during the day, (7) frightening dreams, (8) talking in sleep, (9) sleepwalking, (10) abnormal movement or activity during the night, (11) sleep problems requiring medication, and (12) snoring loudly in all sleeping positions. Each of these conditions was considered to be a problem if the participant responded yes to having either a current or past problem. In addition, a participant was considered as having insomnia currently or in the past if he responded yes to any of the first three conditions (31). Also, an overall sleep disorder index was constructed, where a sleep disorder was defined as yes if a participant responded affirmatively to any of these conditions, either currently or in the past. Each of the 12 conditions, along with insomnia and the sleep disorder index, was dichotomized and analyzed.

Each participant was asked the average number of hours he slept per night. This dependent variable was analyzed in its continuous form.

The presence of PTSD, based on a subset of 49 questions (32) from the MMPI administered at the 1985 examination, was used as an exclusionary criterion for all verified psychological disorders and all sleep disorder variables. This covariate was dichotomized as yes/no using greater than 30 affirmative responses as a positive indicator of PTSD. Of the participants at the 1987 examination with a dioxin assay, 12 were classified as having PTSD (9 Ranch Hands and 3 Comparisons) by this criteria.

Physical Examination Data

Two instruments new to the 1987 examination, the SCL-90-R and the MCMI, were used in the psychological assessment. Participants with PTSD were excluded from the analysis of the variables from the SCL-90-R and the MCMI.

SCL-90-R

The SCL-90-R is a multidimensional self-reported symptom inventory designed to measure symptomatic psychological distress in terms of nine primary symptom dimensions and three global indices of distress (33). Each participant was asked to respond to 90 questions in terms of a 5-point scale: not at all (0), a little bit (1), moderately (2), quite a bit (3), and extremely (4). Responses were grouped into the nine primary symptom categories, and a raw score for a participant for a category was determined by adding the scores of the answered questions in that category and dividing by the number of answered questions in that category. The raw scores were then converted to T-scores (reference scores for a given population norm) for analysis. These nine categories were anxiety, depression, hostility, interpersonal sensitivity, obsessive-compulsive behavior, paranoid ideation, phobic anxiety, psychoticism, and somatization.

Three global indices also were analyzed: the global severity index (GSI), the positive symptom total (PST), and the positive symptom distress index (PSDI). The GSI was defined as the sum of the scores of all answered questions divided by the number of answered questions on the entire test. This index combines information on the number of symptoms and the intensity of distress. The PST was the number of questions to which the

participant responded positively (i.e., 1, 2, 3, or 4). The PSDI was determined by adding the scores of all answered questions and dividing by the PST. This index describes the intensity of the positive symptoms. Each of these indices was also converted to a T-score.

The T-scores from the nine primary symptom categories were classified as normal or abnormal, with abnormal being defined as a T-score of a least 63. Less than 10 percent of the scores for each category were judged to be abnormal, based on this criterion. These symptom categories and indices are described more fully in Appendix H, pages H-1 to H-4.

MCMI

The MCMI (34) is a self-administered test consisting of 175 items and divided into 20 scales. Each of its 20 scales was constructed as an operational measure of a syndrome derived from a theory of personality and psychopathology. The MCMI was not designed to be a general personality instrument to be used for "normal" populations or for purposes other than diagnostic screening or clinical assessment. The 20 scales are organized into three broad categories to reflect distinctions between basic personality patterns, pathological personality disorders, and clinical symptom syndromes. Many of these scales are directly or indirectly correlated. The MCMI scales are described more fully in Appendix H, pages H-5 to H-11.

Basic Personality Patterns. Eight scales from the MCMI focus on everyday ways of functioning that characterize patients even when they are not suffering acute symptom states. These scales reflect relatively enduring and pervasive traits that typify styles of behaving, perceiving, thinking, feeling, and relating to others. These eight scales are schizoid (asocial), avoidant, dependent (submissive), histrionic (gregarious), narcissistic, antisocial (aggressive), compulsive (conforming), and passive-aggressive (negativistic).

Pathological Personality Disorders. Three MCMI scales describe patients who clearly evidence chronic or periodically severe pathology in the overall structure of personality. These scales are schizotypal (schizoid), borderline (cycloid), and paranoid.

Clinical Symptom Syndromes. Nine scales from the MCMI measure reactive disorders, often precipitated by external events, that are of substantially briefer duration than the personality disorders. Six scales—anxiety, somatoform, hypomanic, dysthymic, alcohol abuse, and drug abuse—represent disorders of moderate severity. The other three scales—psychotic thinking, psychotic depression, and psychotic delusions—reflect disorders of marked severity.

Raw scores were derived for each of these scales and were converted to base rate (BR) scores based on known personality and syndrome prevalence data. The BR scores for each of these 20 scales were analyzed as continuous variables. High scores indicated greater emotional illness or psychological abnormality than low scores. Unlike the SCL-90-R, scores were not classified as "normal" for these scales.

Transformations were applied to certain MCMI variables. In particular, a natural logarithm transformation was applied to the schizoid and avoidant scores. This

transformation was performed after adding 1.0 to the avoidant scores because some participants had a score of 0. A square root transformation was used with the dependent, passive-aggressive, and hypomania scores, and a square transformation was applied to the histrionic and compulsive scores. All statistics were converted back to the original units for presentation.

Covariates

Covariates examined in the adjusted statistical analyses of the psychological assessment included age, race, education level (high school, college), current alcohol use (drinks/day), and lifetime alcohol history (drink-years). Age, lifetime alcohol history, and current alcohol use were used in the continuous form for modeling purposes for general linear models and logistic regression analyses. These variables were discretized for presentation of covariate interactions with dioxin.

The lifetime alcohol history and current alcohol use covariates were based on self-reported information from the questionnaire. For lifetime alcohol history, the respondent's average daily alcoholic consumption was determined for various drinking stages throughout his lifetime, and an estimate of the corresponding total number of drink-years (1 drink-year=365 drinks) was derived. The current alcohol use covariate was based on the average drinks per day for the month prior to completing the questionnaire.

Relation to Baseline, 1985, and 1987 Studies

The dependent variables dealing with a history of mental or emotional disorders were analyzed for the Baseline and 1985 studies. However, the variables concerned with sleep disorders, the SCL-90-R, and the MCMI were new to the 1987 study and the serum dioxin analyses. PTSD was an exclusionary criterion for analyses of the 1987 examination data. For the 1985 examination report, PTSD was used as a covariate.

Statistical Methods

Three statistical analysis approaches were used to examine the association between a health endpoint dependent variable and serum dioxin levels. One model related a dependent variable to each Rand Hand's initial dioxin value (extrapolated from current dioxin values using a first-order pharmacokinetic model). A second model related a dependent variable to each Ranch Hand's current serum dioxin value and each Ranch Hand's time since tour. The phrase "time since tour" is often referred to as "time" in discussions of these results. Both of these models were implemented under the minimal and maximal assumptions (i.e., Ranch Hands with current dioxin above 10 ppt and above 5 ppt, respectively). The third model compared the health endpoint dependent variable for Ranch Hands having current dioxin values categorized as unknown, low, and high with Comparisons having background levels. The contrast of the entire Ranch Hand group with the complete Comparison group can be found in the previous report of analyses of the 1987 examination (30). All three models were implemented with and without covariate adjustment. Chapter 4, Statistical Methods, provides a more detailed discussion of the models. Table 9-1 summarizes the statistical analyses performed for the serum dioxin analyses of the psychological assessment. The first part of this table describes the dependent variables; the second part provides a further

TABLE 9-1.

Statistical Analysis for the Psychological Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Psychoses	Q/PE-V	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Alcohol Dependence	Q/PE-V	D	Yes No	AGE,RACE, EDUC	U:LR A:LR
Drug Dependence	Q/PE-V	D	Yes No	--	--
Anxiety	Q/PE-V	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Other Neuroses	Q/PE-V	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Trouble Falling Asleep	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Waking Up During the Night	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Waking Up Too Early and Can't Go Back to Sleep	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Waking Up Unrefreshed	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR

TABLE 9-1. (Continued)

Statistical Analysis for the Psychological Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Involuntarily Falling Asleep During the Day	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Great or Disabling Fatigue During the Day	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Frightening Dreams	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Talking in Sleep	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Sleepwalking	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Abnormal Movement/Activity During the Night	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Sleep Problems Requiring Medication	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Snore Loudly in All Sleeping Positions	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR

TABLE 9-1. (Continued)

Statistical Analysis for the Psychological Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Insomnia	Q-SR	D	Yes No	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Overall Sleep Disorder Index	Q-SR	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
Average Sleep Each Night (hours)	Q-SR	C	--	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Symptom Check List-90-Revised (SCL-90-R) Anxiety	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
SCL-90-R Depression	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
SCL-90-R Hostility	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
SCL-90-R Interpersonal Sensitivity	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
SCL-90-R Obsessive-Compulsive Behavior	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR

TABLE 9-1. (Continued)

Statistical Analysis for the Psychological Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
SCL-90-R Paranoid Ideation	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
SCL-90-R Phobic Anxiety	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
SCL-90-R Psychoticism	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
SCL-90-R Somatization	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR EDUC	U:LR A:LR
SCL-90-R Global Severity Index (GSI)	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
SCL-90-R Positive Symptom Total (PST)	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR
SCL-90-R Positive Symptom Distress Index (PSDI)	PE	D	Abnormal Normal	AGE,RACE, ALC,DRKYR, EDUC	U:LR A:LR

TABLE 9-1. (Continued)

Statistical Analysis for the Psychological Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Millon Clinical Multiaxial Inventory					
Basic Personality Patterns					
Schizoid Score	PE	C	--	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Avoidant Score	PE	C	--	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Dependent Score	PE	C	--	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Histrionic Score	PE	C	--	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Narcissistic Score	PE	C	--	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Antisocial Score	PE	C	--	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Compulsive Score	PE	C	--	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Passive-Aggressive Score	PE	C	--	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM

TABLE 9-1. (Continued)

Statistical Analysis for the Psychological Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Pathological Personality Disorders					
Schizotypal Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Borderline Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Paranoid Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Clinical Symptom Syndromes					
Anxiety Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Somatoform Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Hypomania Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Dysthymia Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Alcohol Abuse Score	PE	C	- -	AGE,RACE, EDUC	U:GLM A:GLM

TABLE 9-1. (Continued)

Statistical Analysis for the Psychological Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Clinical Symptom Syndromes (Continued)					
Drug Abuse Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Psychotic Thinking Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Psychotic Depression Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM
Psychotic Delusion Score	PE	C	- -	AGE,RACE, ALC,DRKYR, EDUC	U:GLM A:GLM

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black
Current Alcohol Use (ALC) (drinks/day)	Q-SR	D/C	0-1 >1

TABLE 9-1. (Continued)

Statistical Analysis for the Psychological Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Lifetime Alcohol History (DRKYR) (drink-years)	Q-SR	D/C	0 >0-40 >40
Education (EDUC)	Q-SR	D	College High School

Abbreviations

Data Source:
MIL--Air Force military records
PE--1987 SCRF psychological examination
Q-SR--1987 NORC questionnaire (self-reported)
Q/PE-V--1987 Questionnaire and physical examination (verified)

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

Statistical Analyses:
U--Unadjusted analyses
A--Adjusted analyses

Statistical Methods:
GLM--General linear models analysis
LR--Logistic regression analysis

description of the candidate covariates. Abbreviations are used extensively in the body of the table and are defined in footnotes.

Appendix H contains graphic displays of individual health endpoint dependent variables versus initial dioxin for the minimal and maximal Ranch Hand cohorts, and individual health endpoint variables versus current dioxin for Ranch Hands and Comparisons. Graphics for dioxin-by-covariate interactions determined by various statistical models are also presented in Appendix H. A guide to assist in interpreting the graphics is found in Chapter 4.

In addition to the participants who were excluded from the psychological assessment due to medical reasons, dependent variable and covariate data were missing for several variables. Table 9-2 provides the number of participants excluded as well as the number of participants with missing data.

RESULTS

Exposure Analysis

Questionnaire Variables

Psychoses (Verified)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analysis of the frequency of Ranch Hands with a verified history of psychoses detected a marginally significant negative association with initial dioxin under the minimal assumption (Table 9-3 [a]: Est. RR=0.64, p=0.099). The percentage of Ranch Hands having verified cases of psychoses for the low, medium, and high initial dioxin categories were 4.6, 1.6, and 2.3 percent. Based on the maximal assumption, there was not a significant association between initial dioxin and Ranch Hands with a verified incidence of psychoses (Table 9-3 [b]: p=0.841).

After incorporating race and education in the model based on the minimal assumption, the negative association between initial dioxin and psychoses was significant (Table 9-3 [c]: Adj. RR=0.57, p=0.042). The maximal adjusted analysis of initial dioxin and psychoses remained nonsignificant (Table 9-3 [d]: p=0.647).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis based on psychoses with current dioxin and time since tour, there was not a significant current dioxin-by-time interaction under either the minimal or the maximal assumption (Table 9-3 [e] and [f]: p=0.351 and p=0.361). Thus, under each assumption, the estimated relative risks of the two time strata did not differ significantly from one another. Similarly, the adjusted analysis exhibited a nonsignificant interaction between current dioxin and time since tour for both the minimal and the maximal assumptions (Table 9-3 [g] and [h]: p=0.332 and p=0.403).

TABLE 9-2.

Number of Participants Excluded and With Missing Data for the Psychological Assessment

Variable	Variable Use	Assumption (Ranch Hands Only) Minimal	Assumption (Ranch Hands Only) Maximal	Categorized Current Dioxin Ranch Hand	Categorized Current Dioxin Comparison
Frightening Dreams	DEP	2	2	3	3
Talking in Sleep	DEP	1	1	1	1
Overall Sleep Disorder Index	DEP	2	2	3	3
12 SCL-90-R Variables	DEP	52	82	88	93
20 MCMI Variables	DEP	2	2	2	2
Current Alcohol Use	COV	3	5	5	0
Lifetime Alcohol History	COV	6	9	9	2
Education	COV	4	5	5	5
Presence of PTSD (1985)	EXC	5	8	8	3
Pre-SEA Anxiety	EXC	1	1	1	2
Pre-SEA Other Neuroses	EXC	4	8	8	6

COV--Covariate (missing data).
DEP--Dependent variable (missing data).
EXC--Exclusion.

TABLE 9-3.

Analysis of Psychoses (Verified)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=516)	Low	130	4.6	0.64 (0.36,1.14)	0.099
	Medium	256	1.6		
	High	130	2.3		
b) Maximal (n=734)	Low	182	0.0	1.04 (0.70,1.54)	0.841
	Medium	369	2.7		
	High	183	1.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=512)	0.57 (0.31,1.04)	0.042	RACE (p=0.145) EDUC (p=0.033)
d) Maximal (n=729)	0.91 (0.59,1.39)	0.647	EDUC (p=0.014)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 9-3. (Continued)

Analysis of Psychoses (Verified)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.351[b]
(n=516)	≤18.6	2.8 (72)	3.1 (128)	5.6 (54)	0.81 (0.41,1.62)	0.552[c]
	>18.6	3.5 (57)	1.6 (129)	0.0 (76)	0.42 (0.11,1.57)	0.197[c]
f) Maximal						0.361[b]
(n=734)	≤18.6	0.0 (105)	3.2 (190)	3.6 (83)	1.27 (0.78,2.08)	0.334[c]
	>18.6	0.0 (78)	2.3 (176)	0.0 (102)	0.85 (0.40,1.81)	0.669[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.332[b]	EDUC (p=0.038)
(n=512)	≤18.6	0.75 (0.37,1.53)	0.425[c]	
	>18.6	0.37 (0.10,1.41)	0.146[c]	
h) Maximal			0.403[b]	EDUC (p=0.016)
(n=729)	≤18.6	1.11 (0.65,1.89)	0.710[c]	
	>18.6	0.75 (0.34,1.65)	0.470[c]	

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 9-3. (Continued)

Analysis of Psychoses (Verified)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	2.7	All Categories		0.377
Unknown	341	1.2	Unknown vs. Background	0.43 (0.15,1.26)	0.125
Low	194	2.1	Low vs. Background	0.76 (0.26,2.25)	0.625
High	185	1.6	High vs. Background	0.60 (0.18,2.03)	0.409
Total	1,503				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	776	All Categories		0.385	AGE (p=0.148)
Unknown	336	Unknown vs. Background	0.50 (0.17,1.47)	0.207	DRKYR (p=0.070)
Low	190	Low vs. Background	0.73 (0.25,2.18)	0.578	EDUC (p=0.086)
High	180	High vs. Background	0.46 (0.13,1.60)	0.223	
Total	1,482				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis of the percentage of participants with a confirmed incidence of psychoses, the contrast of the four current dioxin categories was nonsignificant (Table 9-3 [i]: p=0.377). The adjusted analysis also failed to detect a significant difference among the percentages of verified psychoses of the four current dioxin categories (Table 9-3 [j]: p=0.385).

Alcohol Dependence (Verified)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the unadjusted and adjusted analyses displayed a nonsignificant association between initial dioxin and alcohol dependence in Ranch Hands (Table 9-4 [a-d]: p>0.40 for all analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of alcohol dependence in Ranch Hands, there was not a significant current dioxin-by-time since tour interaction for either the minimal or maximal cohort (Table 9-4 [e] and [f]: p=0.393 and p=0.163). In the adjusted analysis of alcohol dependence in Ranch Hands with current dioxin and time since tour, the current dioxin-by-time interaction was again nonsignificant under both the minimal and the maximal assumptions (Table 9-4 [g] and [h]: p=0.375 and p=0.199). Thus, under both assumptions of the unadjusted and the adjusted analyses, the relative risks of the time strata did not differ significantly from one another.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In both the unadjusted and the adjusted analyses of the frequency of alcohol dependence in Ranch Hands and Comparisons, the simultaneous contrast of the four current dioxin categories was not significant (Table 9-4 [i] and [j]: p=0.563 and p=0.444, respectively).

Drug Dependence (Verified)

Analyses of drug dependence with initial dioxin, current dioxin and time since tour, and Ranch Hands and Comparisons by current dioxin category are not presented due to the sparse number of participants with a confirmed history of drug dependence since the end of their tour. There were no Ranch Hands and only two Comparisons having a verified history of drug dependence (Table 9-5).

Anxiety (Verified)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Based on the minimal assumption, the unadjusted analysis of verified anxiety displayed a nonsignificant association between initial dioxin and the percentage of Ranch Hands with a verified history of anxiety since the end of their tour (Table 9-6 [a]: p=0.159). However, the maximal unadjusted analysis found a significant positive association between initial dioxin and Ranch Hands with a confirmed history of anxiety (Table 9-6 [b]: Est. RR=1.16,

TABLE 9-4.

Analysis of Alcohol Dependence (Verified)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=516)	Low	130	10.8	1.00 (0.76,1.30)	0.999
	Medium	256	5.9		
	High	130	8.5		
b) Maximal (n=734)	Low	182	3.9	1.09 (0.89,1.32)	0.413
	Medium	369	8.9		
	High	183	7.1		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=512)	0.94 (0.71,1.24)	0.666	EDUC (p=0.003)
d) Maximal (n=729)	1.03 (0.83,1.27)	0.821	AGE (p=0.091) EDUC (p=0.002)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 9-4. (Continued)

Analysis of Alcohol Dependence (Verified)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.393[b]
(n=516)	≤18.6	8.3 (72)	5.5 (128)	7.4 (54)	1.14 (0.73,1.78)	0.551[c]
	>18.6	15.8 (57)	5.4 (129)	9.2 (76)	0.89 (0.62,1.27)	0.529[c]
f) Maximal						0.163[b]
(n=734)	≤18.6	3.8 (105)	5.3 (190)	8.4 (83)	1.27 (0.92,1.77)	0.151[c]
	>18.6	7.7 (78)	10.2 (176)	7.8 (102)	0.94 (0.73,1.22)	0.657[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.375[b]	EDUC (p=0.003)
(n=512)	≤18.6	1.09 (0.69,1.71)	0.726[c]	
	>18.6	0.83 (0.57,1.21)	0.329[c]	
h) Maximal			0.199[b]	EDUC (p=0.002)
(n=729)	≤18.6	1.16 (0.82,1.64)	0.403[c]	
	>18.6	0.87 (0.66,1.14)	0.320[c]	

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 9-4. (Continued)

Analysis of Alcohol Dependence (Verified)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	6.0	All Categories		0.563
Unknown	341	7.3	Unknown vs. Background	1.24 (0.75,2.05)	0.404
Low	194	5.2	Low vs. Background	0.85 (0.42,1.72)	0.652
High	185	8.1	High vs. Background	1.38 (0.75,2.53)	0.295
Total	1,503				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	778	All Categories		0.444	AGE (p=0.044) EDUC (p=0.010)
Unknown	339	Unknown vs. Background	1.32 (0.79,2.19)	0.286	
Low	192	Low vs. Background	0.81 (0.40,1.64)	0.557	
High	184	High vs. Background	1.37 (0.74,2.54)	0.323	
Total	1,493				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 9-5.

Analysis of Drug Dependence (Verified)

Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes
Background	783	0.3
Unknown	341	0.0
Low	194	0.0
High	185	0.0
Total	1,503	

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 9-6.

Analysis of Anxiety (Verified)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=515)	Low	129	13.2	1.14 (0.95,1.37)	0.159
	Medium	256	17.6		
	High	130	20.0		
b) Maximal (n=733)	Low	182	14.8	1.16 (1.01,1.34)	0.034
	Medium	368	14.4		
	High	183	19.7		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=511)	1.09 (0.90,1.31)	0.393	EDUC (p=0.019)
d) Maximal (n=728)	1.09 (0.94,1.26)	0.256	EDUC (p=0.009)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 9-6. (Continued)

Analysis of Anxiety (Verified)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.700[b]
(n=515)	≤18.6	15.3 (72)	19.5 (128)	22.2 (54)	1.14 (0.85,1.52)	0.381[c]
	>18.6	8.9 (56)	16.3 (129)	18.4 (76)	1.23 (0.95,1.58)	0.111[c]
f) Maximal						0.418[b]
(n=733)	≤18.6	11.4 (105)	17.4 (190)	19.3 (83)	1.26 (1.02,1.55)	0.034[c]
	>18.6	15.4 (78)	14.9 (175)	16.7 (102)	1.12 (0.92,1.35)	0.263[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.809[b]	EDUC (p=0.022)
(n=511)	≤18.6	1.10 (0.82,1.48)	0.522[c]	
	>18.6	1.15 (0.89,1.50)	0.279[c]	
h) Maximal			0.399[b]	EDUC (p=0.010)
(n=728)	≤18.6	1.18 (0.95,1.48)	0.131[c]	
	>18.6	1.04 (0.85,1.28)	0.679[c]	

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 9-6. (Continued)

Analysis of Anxiety (Verified)

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	781	15.1	All Categories		0.372
Unknown	340	13.2	Unknown vs. Background	0.86 (0.59,1.24)	0.414
Low	194	18.0	Low vs. Background	1.24 (0.82,1.87)	0.316
High	185	17.8	High vs. Background	1.22 (0.80,1.86)	0.359
Total	1,500				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	774	All Categories		0.778	DRKYR (p=0.013) EDUC (p=0.030)
Unknown	335	Unknown vs. Background	0.90 (0.61,1.31)	0.567	
Low	190	Low vs. Background	1.15 (0.75,1.76)	0.518	
High	180	High vs. Background	1.08 (0.70,1.68)	0.727	
Total	1,479				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

p=0.034). Under the maximal assumption, the corresponding frequencies of Ranch Hands with a verified history of anxiety for the low, medium, and high initial dioxin categories were 14.8, 14.4, and 19.7 percent.

After adjusting for education, neither the minimal nor the maximal analysis displayed a significant association between initial dioxin and the frequency of Ranch Hands with a confirmed history of anxiety since the end of their tour (Table 9-6 [c] and [d]: p=0.393 and p=0.256, respectively).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of the verified incidence of anxiety in Ranch Hands since the end of their tour, the interaction between current dioxin and time since tour was not significant for either the minimal or the maximal assumption (Table 9-6 [e] and [f]: p=0.700 and p=0.418). However, under the maximal assumption, there was a significant positive association between current dioxin and verified cases of anxiety for Ranch Hands with 18.6 years or less since the end of their tour (Table 9-6 [f]: Est. RR=1.26, p=0.034). The percentages of Ranch Hands with a confirmed history of anxiety within this time stratum were 11.4, 17.4, and 19.3 percent for the low, medium, and high current dioxin categories.

After an adjustment for education, the analysis of verified anxiety with current dioxin and time since tour did not find a significant current dioxin-by-time interaction under either the minimal or the maximal assumption (Table 9-6 [g] and [h]: p=0.809 and p=0.399).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In both the unadjusted and the adjusted analysis of participants with a history of verified anxiety subsequent to the end of their tour, the simultaneous contrast of the four current dioxin categories was not significant (Table 9-6 [i] and [j]: p=0.372 and p=0.778, respectively).

Other Neuroses (Verified)

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Based on the minimal assumption, the unadjusted analysis did not find a significant association between initial dioxin and the frequency of Ranch Hands with a history of conditions in the "other neuroses" category since the end of their tour (Table 9-7 [a]: p=0.268). In contrast, the maximal unadjusted analysis did detect a significant positive association between initial dioxin and Ranch Hands with a history of other neuroses (Table 9-7 [b]: Est. RR=1.17, p=0.004). The percentage of Ranch Hands with documented cases of other neuroses since the end of their tour became larger with increasing initial dioxin (low, 31.5%; medium, 43.7%; high, 46.2%).

After the inclusion of lifetime alcohol history and education in the model, the adjusted analysis did not find a significant association between initial dioxin and Ranch Hands with a history of other confirmed neuroses for either the minimal or the maximal cohort (Table 9-7 [c] and [d]: p=0.673 and p=0.331).

TABLE 9-7.
Analysis of Other Neuroses (Verified)

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I)[a]	p-Value
a) Minimal (n=512)	Low	128	39.1	1.08 (0.94,1.25)	0.268
	Medium	255	45.9		
	High	129	46.5		
b) Maximal (n=726)	Low	178	31.5	1.17 (1.05,1.30)	0.004
	Medium	366	43.7		
	High	182	46.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=502)	1.03 (0.89,1.20)	0.673	DRKYR (p=0.003) EDUC (p=0.001)
d) Maximal (n=712)	1.06 (0.94,1.19)	0.331	DRKYR (p<0.001) EDUC (p<0.001)

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

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 9-7. (Continued)

Analysis of Other Neuroses (Verified)

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.294[b]
(n=512)	≤18.6	36.1 (72)	46.1 (128)	53.7 (54)	1.20 (0.95,1.51)	0.136[c]
	>18.6	38.2 (55)	45.3 (128)	45.3 (75)	1.02 (0.84,1.23)	0.874[c]
f) Maximal						0.082[b]
(n=726)	≤18.6	30.8 (104)	42.6 (190)	47.0 (83)	1.30 (1.09,1.53)	0.003[c]
	>18.6	33.3 (75)	47.4 (173)	40.6 (101)	1.06 (0.92,1.23)	0.420[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.282[b]	DRKYR (p=0.002)
(n=502)	≤18.6	1.15 (0.90,1.47)	0.252[c]	EDUC (p=0.002)
	>18.6	0.97 (0.79,1.19)	0.765[c]	
h) Maximal			0.112[b]	DRKYR (p<0.001)
(n=712)	≤18.6	1.18 (0.98,1.41)	0.075[c]	EDUC (p<0.001)
	>18.6	0.97 (0.83,1.14)	0.731[c]	

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

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.